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***Real life long-term efficacy and safety of rhGH therapy
in children with SHOX deficiency***

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Short Title: Long-term efficacy and safety of rhGH in SHOX-D.

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Abstract

Objective: This Italian survey aims to evaluate real-life long-term efficacy and safety of rhGH therapy in children with short stature homeobox-containing gene deficiency disorders (SHOX-D) and to identify potential predictive factors influencing response to rhGH therapy.

Design and Methods: This is a national retrospective observational study collecting anamnestic, anthropometric, clinical, instrumental and therapeutic data in children and adolescents with a genetic confirmation of SHOX-D treated on rhGH. Data were collected at the beginning of rhGH therapy (T0), yearly during the first 4 years of rhGH therapy (T1, T2, T3, T4) and at near-final height (nFH) (T5), when available.

Results: 117 SHOX-D children started rhGH therapy (initial dose 0.23 ± 0.04 mg/kg/week) at a mean age of 8.67 ± 3.33 years (74% prepubertal), 99 completed the 1st year of treatment, and 46 reached nFH. During rhGH therapy, growth velocity (GV) SDS and height (H) SDS improved significantly. Mean H SDS gain from T0 was $+1.14 \pm 0.58$ at T4 and $+0.80 \pm 0.98$ at T5. Both patients carrying mutations involving intragenic SHOX region (group A) and ones with regulatory region defects (group B) experienced a similar beneficial therapeutic effect. The multiple regression analysis identified the age at the start of rhGH treatment ($\beta -0.31$, $p 0.030$) and the GV during the first year of rhGH treatment ($\beta 0.45$, $p 0.008$) as main independent predictor factors of height gain. During rhGH therapy, no adverse event of concern was reported.

Conclusions: Our data confirm the efficacy and safety of rhGH therapy in SHOX-D children, regardless the wide variety of genotype.

Significance Statement

Among children with idiopathic short stature, the prevalence of short stature homeobox-containing gene (SHOX) deficiency disorders (SHOX-D) is near to 1/1.000-2.000 (1.1-15%) with a wide phenotypic spectrum. Current guidelines support recombinant human growth hormone (rhGH) therapy in SHOX-D children, but long-term data are still few. Our real-life data confirm the efficacy and safety of rhGH therapy in SHOX-D children, regardless the wide variety of genotype. Moreover, rhGH therapy seems to blunt SHOX-D phenotype. The response to rhGH in the first year of treatment and the age when rhGH was started significantly impact the height gain.

Introduction

The short stature homeobox-containing (SHOX) gene, located in pseudo-autosomal region 1 of the short arms of the X and Y chromosomes, encodes a homeodomain transcription factor involved in the regulation of longitudinal growth and acting in chondrocyte proliferation and differentiation in the growth plate. SHOX gene escapes X inactivation, requiring the expression of both alleles. Its homozygous deficiency causes Langer type mesomelic dysplasia, while its haploinsufficiency (SHOX-D) ranges into a large phenotypic spectrum and heterogeneity: from normal or short stature with or without dysmorphic features and/or normal body proportions to mesomelic skeletal dysplasia, as in Léry-Weill dyschondrosteosis (LWD) (1, 2). The most frequent (around 80%) SHOX mutations encompass deletions in the SHOX gene itself or in the regulatory enhancer regions downstream or upstream of the SHOX gene, leaving the gene itself intact (3). Intragenic microdeletions and point mutations occur in the rest of the cases, but, over the past years, advancements in genetics suggested that also duplications in enhancer regions inhibit the proper expression of the gene and could cause SHOX-D phenotype (1, 4). Up to now, more than 1200 unique allelic variants have been reported in the SHOX database (5) and among children and adolescents with idiopathic short stature (ISS) the prevalence of SHOX-D is documented to range between 1.1 and 16.9% (6), as confirmed by recent Italian data [1/1.000-2.000 (1.1-15%)] (7). Nevertheless, no clear and consonant data clarify the genotype-phenotype association in SHOX-D yet and many authors still claim the indistinguishability of phenotypes generated from enhancer mutations and the ones from single nucleotide variants and deletions affecting the SHOX coding region (8).

Recombinant human growth hormone (rhGH) therapy is already approved for use in patients with SHOX-D in the USA, Europe and other countries (9) and it seems to have a growth-promoting activity similar to patients with Turner syndrome (TS) (10). Nonetheless, to date, data on the long-term effectiveness of rhGH treatment in this category of paediatric patients are still too scarce (10-13) and no conclusive data indicate whether different causative genotype could influence the response to rhGH therapy (14, 15).

The aim of our study is to report the real-life Italian long-term experience about the efficacy and safety of rhGH therapy in SHOX-D children and adolescents. Therefore, we collected data from several tertiary paediatric endocrine centres, affiliated to the Italian Society of Pediatric Endocrinology and Diabetology Study Group on Growth Factors and Puberty. Moreover, basing on the large national cohort, we would like to identify the potential predictive factors influencing the response to rhGH therapy, including different causative genotype.

Materials and Methods

This is a national retrospective longitudinal cohort study enrolling patients with a genetically confirmed diagnosis of SHOX-D, treated on rhGH therapy at 14 Italian Pediatric Endocrine Clinics (Modena, Turin, Bologna, Genoa, Firenze, Naples, Milan, Reggio Emilia, Alessandria, Varese, Messina, Gallipoli, Trieste, Bari) from January 2010 to June 2022. Patients affected by other endocrine diseases (e.g. central precocious puberty, congenital adrenal hyperplasia, hypothyroidism, type 1 diabetes mellitus), organic brain lesion, systemic diseases as well as taking drugs interfering with height growth, body weight, and glucose metabolism (e.g. GnRH analogues, corticosteroids, chemotherapies) were excluded.

All anthropometric, laboratory, instrumental and therapeutic data were collected by experienced pediatric endocrinologists at baseline, at the beginning of rhGH treatment [Time 0 (T0)], yearly on rhGH therapy [T1, T2, T3 and T4] and at near-final height (nFH) [T5], when available, and were anonymously recorded in a database using an alphanumeric and progressive identification code.

None of enrolled patients was previously involved in other protocols and/or publications.

The study was conducted in agreement with the Declaration of Helsinki and was approved by the Ethical Committee of the coordinator centre [Modena - Protocol number 0016074/2019].

Parental written informed consent and patient assent were obtained at recruitment and before starting the data collection.

Anthropometric measures

All recruited patients underwent a complete past medical history [recorded data: chronological age (CA), gender, ethnicity, gestational age and birth anthropometric data, concomitant medical conditions, results of SHOX genetic testing]. The anthropometric measurements were performed at any study time according to the Anthropometric Standardization Reference Manual in every centre by well-trained paediatric endocrine clinicians (16) and they included: standing height (H), measured to the nearest 0.1 cm with a calibrated well-mounted Harpenden's stadiometer (Crymych, UK), compared with age-matched reference values and expressed as standard deviation score (H SDS) (17); sitting height, measured from the highest point of the head to the sitting surface; arm SPAN, measured from the fingertips of one hand to the other with the arms raised parallel to the ground (18); body weight, measured to the nearest 0.1 kg with a calibrated scale, and pubertal staging, assessed using the Marshall and Tanner maturity scale (19,20). Body mass index (BMI) was calculated by dividing weight in kg by square of the height (m^2) and was standardized to SDS (BMI SDS) according to age using appropriate Italian chart (17). Near-final height (nFH) was defined when growth velocity (GV) was less than 1 cm/year during last 6 months and/or when the hand and wrist X-ray showed a process of

epiphyseal fusion (BA > 16 years in males, >14 years in females) (21). Height gain was defined as the difference between H at T4 or at T5 and H at the beginning of treatment (T0) and expressed in SDS. At each study time, the Rappold's scoring system, evaluating the presence of any combination of body disproportions [reduced arm SPAN/H ratio (<96.5%), increased sitting H/H ratio (>55.5%)], the above-average BMI, the presence of Madelung deformity, of cubitus valgus, of short or bowed forearms and of dislocation of the ulna at the elbow or of muscular hypertrophy, was calculated and considered as an indicator of SHOX-D when ≥ 4 (22). Sitting H/H ratio was compared with age- and gender-matched reference values (23) and expressed both as absolute number and as its standard deviation score (sitting H/H ratio SDS). The presence of other SHOX-D-related clinical features as tibial varus, muscular pseudo-hypertrophy and ogival palate was also verified and collected at each study time.

All patients were submitted to rhGH treatment according to the Italian Agency for Drugs (AIFA) guidelines (24).

Biochemical analysis

Fasting glucose, insulin and IGF1 values were measured by local laboratories using specific commercially available kits at each study time. IGF1 levels were expressed as SDS: in our database, each IGF-1 measurement has been documented with its specific age- and gender-adjusted reference ranges, constituting two standard deviations (SD) above and below the age and gender adjusted mean IGF-1, respectively. IGF-1 SDS was calculated as the difference between measured IGF-1 and mean IGF-1, divided by the SD (25). Insulin resistance (IR) was defined by homeostatic model assessment index (HOMA index), compared to specific pediatric percentiles according to gender and pubertal stage (26), and if fasting glucose/insulin ratio (FGIR) was <7 (27).

Genetic analysis of SHOX

The genetic analysis of SHOX gene was performed at different Italian centres according to local clinical practice.

Diagnostic imaging

The skeletal maturation was assessed on roentgenograms of the non-dominant hand and wrist and the bone age (BA) was determined according to the method of Greulich and Pyle (28). The presence of radiological dysmorphic features and bone abnormalities including carpal wedging (pyramidisation of the carpal row), distal radial lucency, shortness of 4th and/or 5th metacarpals, the shape of distal radial epiphysis (flat, round, convex, triangular or trapezoidal) and/or Madelung deformity of the wrist were evaluated by well-trained paediatric endocrine clinicians.

Statistical analysis

Data were checked for normal distribution using the Kolmogorov-Smirnov test. Continuous data are reported as mean \pm standard deviation (SD), while categorical ones as percent values. The statistical analysis was performed in total study population as well as in groups defined according to SHOX-D genotype: patients carrying SHOX intragenic mutations or deletions (group A) and patients with SHOX enhancers mutations (group B). Between-groups comparisons were performed using Mann-Whitney U test (for two numerical variables), Kruskal-Wallis ANOVA (for more than two numerical variables) and Pearson χ^2 test (for percent values). The Friedman ANOVA test was used for longitudinal comparison of variables in total population as well as in each group. Spearman correlation was used to identify the association between variables. A significative model (model SE 0.40, R^2 0.24, p 0.005) comprising height gain SDS at T4 as dependent variable, and age when rhGH was starting, rhGH starting dose, growth velocity during the first and the second year of rhGH treatment as independent variables was used to perform the multiple regression analysis.

For each test, statistical significance was for $p < 0.05$.

The statistical analysis was performed using the STATISTICA™ software (StatSoft Inc., Tulsa, OK, USA).

Results

Baseline data

The initial total population comprise 117 children and adolescents (93% Caucasian, 74% prepubertal and 52% male) with a confirmed genetic diagnosis of SHOX deficiency, 75 with intragenic point mutation or deletion of SHOX gene and 42 with SHOX enhancers mutations (Table 1 and 2). Anthropometric data at birth were normal (gestational age 38.71 ± 1.90 weeks, birth weight 3008.51 ± 534.09 gr, length 48.22 ± 6.04 cm). rhGH was started at a mean age of 8.67 ± 3.33 years at a dose of 0.23 ± 0.04 mg/kg/week (range 0.12 – 0.35 mg/kg/week). Before starting rhGH treatment, patients showed a growth impairment (H -2.37 ± 0.67 SDS, H adjusted for TH -1.11 ± 1.11 and GV -1.37 ± 1.65 SDS), mild bone age delay (BA – CA: -1.07 ± 1.09 years) as well as slight SHOX-D stigmata: arm SPAN/height ratio equal to 0.97 ± 0.07 , sitting height/height ratio 0.56 ± 0.02 and its SDS 2.19 ± 1.27 and mean Rappold's score 7.51 ± 4.86 (range 0 – 24). Other phenotypic SHOX-D features as tibial varus, muscular pseudohypertrophy, high arched palate and radiological bone abnormalities were encountered in 34%, 45%, 17% and 46% of total population, respectively. In total population, IGF-1 SDS was -0.99 ± 0.93 . The baseline clinical presentation was uniform among groups, regardless different genotype (table 2).

Efficacy

In our cohort, rhGH therapy lasted about 5.94 ± 2.00 years (range 1.25 – 11.30 years) and it led to an overall height gain of $+0.80 \pm 0.98$ SDS from baseline until the achievement of nFH. Along therapy patients experienced a significant improvement of GV SDS, especially during the first two years of treatment, and a concomitant gradual increase of H SDS (table 1 and figures 1 and 2). The therapy did not affect BMI SDS and the bone delay reduced gradually over follow-up (table 1). Globally, rhGH seemed to longitudinally prevent a worsening of both body proportions and Rappold's score and to limit the increase of prevalence of clinical SHOX-D features as tibial varus, muscular pseudohypertrophy and high arched palate (table 1). The mean dose of rhGH did not change significantly along follow-up (table 1). At the time of the analysis, among 117 SHOX-D children and adolescents started on rhGH at T0, 18 did not complete the 1st year of treatment, other 9 the second year, other 18 the third year and other 14 the fourth year of rhGH. No therapeutic drop-out was registered along study-time. By now, 46 patients reached nFH (nFH group). When the longitudinal analysis was performed exclusively in nFH group, results were mostly overlapping the ones referred to total population: a notable increasing of H SDS and GV SDS was confirmed across rhGH, together with a statistical amelioration of body proportion, specifically a reduction of sitting height/H ratio SDS and a stability of Rappold's score (Table 3). Unlike total cohort, in nFH group BMI SDS increased at T5. Moreover, a little but significant increase of rhGH dose was detected from the third year of treatment (Table 3). Baseline anthropometric data did not differ between total and nFH group.

A beneficial effect on growth of rhGH was demonstrated both in patients carrying mutations involving SHOX exons (group A) and in ones with SHOX enhancer mutations (Group B), as shown in table 2 (group A vs. B: H gain at T4 $+1.11 \pm 0.59$ vs. $+1.17 \pm 0.59$ SDS, p 0.64; overall H gain $+0.88 \pm 0.96$ vs. $+0.67 \pm 1.02$ SDS, p 0.29; mean rhGH duration 5.82 ± 2.03 vs. 6.12 ± 2.00 years, p 0.34). Even if short stature was similar in both groups, group B presented milder phenotype, as expressed in a persistently lower Rappold's score in group B than in group A along follow-up, especially reaching a statistical significance on therapy (at T3 and at T4) (table 2). Moreover, only in group B, sitting height/height ratio, but not its SDS, ameliorated during rhGH therapy and a significant increase of rhGH dosage has been documented along study time. This dose adequacy could be consequent to a significant decrease of H SDS and of growth velocity SDS in group B than in A during the second year of rhGH treatment (table 2). Along rhGH treatment, IGF-1 SDS increase in both groups.

In our cohort, H gain at T4 correlated with GV during first year (r 0.30), second year (r 0.37), third year (r 0.47) and fourth year (r 0.32) of rhGH treatment. Similarly, the overall H gain correlated with GV during the first (r 0.40), second (r 0.35) and third year (r 0.35) of rhGH treatment, but not with age when rhGH treatment was started (r -0.15) and not with the initial rhGH dose (r -0.26).

Nevertheless, the multiple regression analysis (model SE 0.40, R2 0.24, p 0.005) identified age when rhGH was started (β -0.31, p 0.030) and growth velocity during the first year of rhGH treatment (β 0.45, p 0.008) as main independent predictor factors of height gain SDS at T4.

Safety

IGF-1 levels increased along treatment and were significantly superior in group A than B at T4. Even if some patients experienced high IGF-1 SDS on therapy (IGF-1 SDS above 2 SDS in 12.5% of patients at T1, in 14% at T2, in 16.3% at T3 and in 18% at T4, χ^2 8,5, p 0.67), no related discontinuation, even transient, was documented, and no other adverse event of concern was reported.

A condition of initial insulin-resistance was described already in 12% (8/68) of patients before the start of rhGH therapy and this prevalence did not change significantly on treatment [T1: 11/84 (13%); T2: 12/73 (16%); T3: 11/58 (19%); T4 13/52 (25%), χ^2 6.56, p 0.58).

Discussion and Conclusion

Our data strongly confirm the efficacy of rhGH in SHOX-D patients. In fact, rhGH therapy led to an overall height gain of $+0.80 \pm 0.98$ SDS from baseline until the achievement of nFH. In the last years, the access to rhGH treatment become gradually easier for SHOX-D children, firstly due to earlier clinical suspicion and more rapid genetic diagnosis than before and, secondly, due to the authorization of rhGH treatment in SHOX-D patients independently from the presence of GH deficiency. If not treated, SHOX-D final height is estimated around 2 SDS below the mean. If treated, about the 40% of SHOX-D patients on rhGH therapy seemed to reach an appropriate FH in contrast to 4% of non-treated ones (4). First supporting data came from the use of rhGH in patients with TS, a condition that is associated with the loss of one SHOX gene because of the numerical or structural aberration of the X chromosome (29,30). Subsequently, several studies supported short-term rhGH efficacy in SHOX-D (30-32-). Nevertheless, up to now, long-term data are still lacking and in literature, to our knowledge, no more than 200 SHOX-D patients treated on rhGH and who achieved FH or nFH have been described (10-13). In 2017, data from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) observational study and clinical trial reported near-FH of 90 and 28 SHOX-D patients, respectively: height gain was $+0.83$ SDS after 4.4 years of rhGH for the full GeNeSIS cohort ($+1.19$ SDS if patients were prepubertal at the beginning of the treatment) compared with $+1.25$ SDS for patients in the clinical trial after 6 years of therapy (13). These data are entirely in line with our real-life experience despite differences between the cohorts: a major prevalence of mutations in SHOX regulatory regions (36% vs. 4%) and a lower dose of initial rhGH (0.23 ± 0.04 vs. 0.30 ± 0.09 mg/kg/week) characterized our cohort respect to GeNeSIS's. Recently, also Dantas and colleagues published data on

adult height in 18 SHOX-D patients that received rhGH therapy (10 on combined therapy with GnRH analogues) and in 13 followed without treatment: a negative median change in height from baseline to adult height of -0.8 SDS was documented in these latter, while the treated ones showed a median positive change in height of about $+0.6$ SDS (11). Our results are more promising than Dantas's linked to a larger studied population and despite the use of a lower median dose of rhGH (0.24 vs. 0.34 mg/kg/week). In fact, in our report, the real-life dose of rhGH used in SHOX-D is lower respect to the one that should be offered and usually overlapping Turner's indication: at least 0.35 mg/kg/week. In SHOX-D, the effect of rhGH therapy seems to be associated with the induction of the same intracellular signalling response triggered by endogenous GH and, in most cases, with an increased serum concentrations of the GH-dependent peptides as IGF-1. Thus, a strong dose-dependent growth-promoting effect of rhGH is expected (8). Analysing our data, we could justify the use of a general low-medium rhGH dose due to the retrospective design of the study itself: many patients with long follow-up may started rhGH as a replacement rather than a pharmacological therapy, maybe because they met the criteria to be classified as GH deficient. In the same way, we can only speculate that it is also the cause of the lack of a dose adjustment across follow-up, together with the real practice of each clinician maybe supported by a good anthropometric and biochemical response to the rhGH therapy itself among her/his patients, as shown in our report. In fact, despite the use of a low-medium rhGH dose, we demonstrated a significant increase of IGF-1 SDS in response to rhGH therapy. Moreover, in our cohort, the young age at the beginning of rhGH rather than the initial dosage seems to influence the long-term growth improvement, as revealed by the results of the multi-regression analyses. An earlier initiation of rhGH therapy seems to strengthen growth in the prepubertal period and to preserve it from a gradual worsening in puberty, as occurred in untreated SHOX-D patients (13). As in other rhGH therapeutic indications, the main part of the catch-up growth happened in the first two years of treatment (13,30, 32), but our current data demonstrated its long-term persistence: in fact, in our cohort, height gain after 4 years of rhGH treatment correlated with the growth velocity not only on the first two years but also on the third and the fourth year of treatment.

Other factors could affect treatment-response as intrinsic individual sensibility and SHOX-D genotype as well as external factors, including therapeutic adherence, concomitant replacement of other hormones, nutritional status and duration of treatment. In 2015, Donze SH and colleagues published data collected in a retrospective study from 130 children and adolescents (72 with SHOX point mutations or deletions, 44 with SHOX enhancer deletion, and 14 with duplications of SHOX or its enhancer) of whom 52 were treated with rhGH (37/72 in the first group, 12/44 in the second group and 3/14 in the last group): patients with SHOX enhancer deletion seemed to be equally short but less disproportionate in comparison to patients with SHOX point mutations or deletions, and they showed

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a greater response to rhGH (14). Our data only partially confirm Donze's finding, while are in line with other publication (33): in fact, we document that children carrying mutations involving SHOX enhancer seemed to present a milder phenotype, but not a less severe growth impairment at baseline, than ones with intragenic mutations. The amelioration of sitting height/height ratio in this group on rhGH therapy is only apparent because, considering the strong influence of age on this ratio, SDS is more reliable than the absolute values and, also patients with SHOX enhancer deletion, its SDS did not change along therapy. Nevertheless, at the same time, we prove a similar response to rhGH in the two groups not only in clinical parameters (improvement of H SDS, GV SDS and H gain SDS), but also in biochemical ones (increase of IGF-1 SDS). The difference in IGF-1 SDS at T4 between the two groups seemed, in our opinion, to be linked to a possible difference in the rate of puberty progression rather than to inter-groups difference of rhGH-sensibility. In their paper, Donze and colleagues speculate that, if rhGH promotes expression of SHOX via downstream GH-dependent transcription factors, the presence of two intact copies of SHOX in patients with enhancer mutation may cause a higher responsiveness to rhGH (14). Our population is wider than Donze's, but still genetically heterogeneous and there is still a relatively small number of patients within each variant that do not allow us for individual variant comparisons. We believe that only the study of the residual functionality of SHOX in each genetic variants could explain the phenotype in terms of degree of skeletal disproportion, in terms of clinical presentation and/or in terms of growth impairment as well as in terms of therapeutic response. By now, we can only conclude that rhGH therapy seems to blunt SHOX-D phenotype limiting a worsening of the body proportions and of the clinical SHOX-D stigmata (Rappold's score, tibial varus, muscular pseudohypertrophy and high arched palate) that usually became more pronounced with age in untreated SHOX-D patients (8). This effect could be mediated by the rhGH-related improvement of linear growth, especially involving long bones.

Concerning the safety of rhGH, our results did no evidence any new or unexpected rhGH-related short-term and long-term adverse events in SHOX-D patients (34).

Our current study presents several limitations, especially the possible variability of registered parameters due to the enrolment of patients in different clinical centres and the absence of a uniform population at each time of study due to its retrospective design. Nevertheless, at the same time, these conditions could be also considered as strengths of the study itself because letting us to study longitudinally a wide SHOX-D population (national cohort) in a real-life clinical setting. To date, the retrospective design of the study imposed us to collect some parameters as Rappold's score currently used in the clinical practice but discussed in literature if reliable (35). Some limitations could be overcome in a prospective phase of the study that is already scheduled.

Our data confirm the efficacy and safety of rhGH therapy in SHOX-D children, regardless the wide variety of genotype. Moreover, the response to rhGH in the first year of treatment and the age when rhGH was started significantly impact the overall height gain.

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Declaration of Interest

Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contribution statement

L.I. and P.B. conceptualized the study, analysed and interpreted the data and wrote the manuscript. All the authors acquired their patient data, contribute to fulfil the final database and approved the final version, and all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- 1 Marchini A, Ogata T, Rappold GA. A Track Record on SHOX: From Basic Research to Complex Models and Therapy. *Endocr Rev* 2016 **37(4)** 417-48. ([https://doi: 10.1210/er.2016-1036](https://doi.org/10.1210/er.2016-1036))
- 2 Mastromauro C, Chiarelli F. Novel Insights Into the Genetic Causes of Short Stature in Children. *touchREV Endocrinol* 2022 **18(1)** 49-57. ([https://doi: 10.17925/EE.2022.18.1.49](https://doi.org/10.17925/EE.2022.18.1.49))
- 3 Kang MJ. Novel genetic cause of idiopathic short stature. *Ann Pediatr Endocrinol Metab* 2017 **22(3)** 153-157. (<https://doi.org/10.6065/apem.2017.22.3.153>)
- 4 Fanelli A, Vannelli S, Babu D, Mellone S, Cucci A, Monzani A, Al Essa W, Secco A, Follenzi A, Bellone S, Prodam F, Giordano M. Copy number variations residing outside the SHOX enhancer region are involved in Short Stature and Léri-Weill dyschondrosteosis. *Mol Genet Genomic Med* 2022 **10(1)** e1793. (<https://doi.org/10.1002/mgg3.1793>)
- 5 <https://databases.lovd.nl/shared/genes>
- 6 Kurnaz E, Savaş-Erdeve S, Çetinkaya S, Aycan Z. SHOX gene deletion screening by FISH in children with short stature and Madelung deformity and their characteristics. *J Pediatr Endocrinol Metab* 2018 **31(11)** 1273-1278. (<https://doi.org/10.1515/jpem-2018-0038>)
- 7 Orso M, Polistena B, Granato S, Novelli G, Di Virgilio R, La Torre D, D'Angela D, Spandonaro F. Pediatric growth hormone treatment in Italy: A systematic review of epidemiology, quality of life, treatment adherence, and economic impact. *PLoS ONE* 2022 **17(2)** e0264403. (<https://doi.org/10.1371/journal.pone.0264403>)
- 8 Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. *Horm Res Paediatr* 2011 **75(2)** 81-9. (<https://doi.org/10.1159/000324105>)
- 9 Savage, M.O. The Changing Face of Paediatric Human Growth Hormone Therapy. *Endocrines* 2022 **3** 419–427. (<https://doi.org/10.3390/endocrines3030033>)
- 10 Blum WF, Ross JL, Zimmermann AG, Quigley CA, Child CJ, Kalifa G, Deal C, Drop SLS, Rappold G, Cutler GB Jr. GH treatment to final height produces similar height gains in patients with SHOX deficiency and turner syndrome: results of a multicenter trial. *J Clin Endocrinol Metab* 2013 **98(8)** E1383-92. (<https://doi.org/10.1210/jc.2013-1222>)
- 11 Dantas NCB, Funari MFA, Vasques GA, Andrade NLM, Rezende RC, Brito V, Scalco RC, Arnhold IJP, Mendonca BB, Jorge AAL. Adult height of patients with SHOX haploinsufficiency with or without GH

therapy: A Real-World Single-Center Study. *Horm Res Paediatr* 2022 **95(3)** 264-274. (<https://doi.org/10.1159/000524374>)

12 Blum WF, Cao D, Hesse V, Fricke-Otto S, Ross JL, Jones C, Quigley CA, Binder G. Height gains in response to growth hormone treatment to final height are similar in patients with SHOX deficiency and Turner syndrome. *Horm Res* 2009 **71(3)** 167–72. (<https://doi.org/10.1159/000197874>)

13 Benabbad I, Rosilio M, Child CJ, Carel JC, Ross JL, Deal CL, Drop SLS, Zimmermann AG, Jia N, Quigley CA, Blum WF. Safety outcomes and near-adult height gain of growth hormone treated children with SHOX deficiency: data from an observational study and a clinical trial. *Horm Res Paediatr* 2017 **87(1)** 42–50. (<https://doi.org/10.1159/000452973>)

14 Donze SH, Meijer CR, Kant SG, Zandwijken GR, van der Hout AH, van Spaendonk RM, van den Ouweland AM, Wit JM, Losekoot M, Oostdijk W. The growth response to GH treatment is greater in patients with SHOX enhancer deletions compared to SHOX defects. *Eur J Endocrinol* 2015 **173(5)** 611-21. (<https://doi.org/10.1530/EJE-15-0451>)

15 Chen J, Wildhardt G, Zhong Z, Roth R, Weiss B, Steinberger D, Decker J, Blum WF & Rappold G. Enhancer deletions of the SHOX gene as a frequent cause of short stature: the essential role of a 250 kb downstream regulatory domain. *Journal of Medical Genetics* 2009 **46** 834–839. (<https://doi.org/10.1136/jmg.2009.067785>)

16 Lohman TG, Roche AF, Martorell R, eds. Anthropometric Standardization Reference Manual. Human Kinetics Books, Champaign IL, 1988

17 Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, Cerutti F, Gargantini L, Greggio N, Tonini G, Cicognani A. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). *J Endocrinol Invest* 2006 **29,7** 581–593. (<https://doi.org/10.1007/BF03344156>)

18 Bogin B, Varela-Silva MI. Leg length, body proportion, and health: a review with a note on beauty. *Int J Environ Res Public Health* 2010 **7** 1047–75. (<https://doi.org/10.3390/ijerph7031047>)

19 Marshall WA, Tanner JM. Variations in Pattern of Pubertal Changes in Girls. *Arch Dis Child* 1969 **44(235)** 291-303. (<https://doi.org/10.1136/adc.44.235.291>)

20 Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970 **45(239)** 13-23. (<https://doi.org/10.1136/adc.45.239.13>)

21 Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, Chernausk SD, Savage MO, Wit JM. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society,

and the European Society for Paediatric Endocrinology Workshop. *J Clin Endocrinol Metab* 2008 **93(11)** 4210-7. ([https://doi: 10.1210/jc.2008-0509](https://doi.org/10.1210/jc.2008-0509))

22 Rappold G, Li WF, Shavrikova EP, Crowe BJ, Roeth R, Quigley CA, Ross JL, Niesler B. Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. *J Med Genet* 2007 **44(5)** 306-13. (<https://doi.org/10.1136/jmg.2006.046581>)

23 Fredriks AM, van Buuren S, van Heel WJM, Dijkman-Neerincx RHM, Verloove-Vanhorick SP, Wit JM. Nationwide age references for sitting height, leg length, and sitting/height ratio, and their diagnostic value for disproportionate growth disorders. *Arch Dis Child* 2005 **90** 807-812. ([https://doi: 10.1136/adc.2004.050799](https://doi.org/10.1136/adc.2004.050799))²⁴https://www.aifa.gov.it/documents/20142/1491706/Determina_AIFA_390_2021_modifica_nota_39.pdf

25 Tirosh A, Toledano Y, Masri-Iraqi H, Eizenberg Y, Tzvetov G, Hirsch D, Benbassat C, Robenshtok E, Shimon I. IGF-I levels reflect hypopituitarism severity in adults with pituitary dysfunction. *Pituitary* 2016 **19(4)** 399-406. ([https://doi: 10.1007/s11102-016-0718-1](https://doi.org/10.1007/s11102-016-0718-1))²⁶ d'Annunzio G, Vanelli M, Pistorio A, Minuto N, Bergamino L, Iafusco D, Lorini R. Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes. Insulin resistance and secretion indexes in healthy Italian children and adolescents: a multicentre study. *Acta Biomed* 2009 **80(1)** 21-8

27 Silfen ME, Manibo AM, McMahon DJ, Levine LS, Murphy AR, Oberfield SE. Comparison of Simple Measures of Insulin Sensitivity in Young Girls with Premature Adrenarche: The Fasting Glucose to Insulin Ratio May Be a Simple and Useful Measure. *J Clin Endocrinol Metab* 2001 **86(6)** 2863-8. (<https://doi.org/10.1210/jcem.86.6.7537>)

28 Greulich WW. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, CA: Stanford University Press, 1959. <http://www.abebooks.com/book-search/title/radiographic-atlas-skeletal-development-hand-wrist>

29 Li P, Cheng F, Xiu L. Height outcome of the recombinant human growth hormone treatment in Turner syndrome: a meta-analysis. *Endocr Connect* 2018 **7(4)** 573-583. (<https://doi.org/10.1530/EC-18-0115>)

30 Blum WF, Crowe BJ, Quigley CA, Jung H, Cao D, Ross JL, Braun L, Rappold G. Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: two-year results of a randomized, controlled, multicenter trial. *J Clin Endocrinol Metab* 2007 **92** 219–228. (<https://doi.org/10.1210/jc.2006-1409>)

31 Munns CF, Berry M, Vickers D, Rappold GA, Hyland VJ, Glass IA, Batch JA. Effect of 24 months of recombinant growth hormone on height and body proportions in SHOX haploinsufficiency. *J Pediatr Endocrinol Metab* 2003 **16** 997–1004. (<https://doi.org/10.1515/jpem.2003.16.7.997>)

Iughetti L, Vannelli S, Street ME, Pirazzoli P, Bertelloni S, Radetti G, Capone L, Stasiowska B, Mazzanti L, Gastaldi R, Maggio MC, Predieri B. Impaired GH secretion in patients with SHOX deficiency and efficacy of recombinant human GH therapy. *Horm Res Paediatr* 2012 **78(5-6)** 279-87. (<https://doi.org/10.1159/000345354>)

33 Shapiro S, Klein GW, Klein ML, Wallach EJ, Fen Y, Godbold JH, Rapaport R. SHOX gene variants: growth hormone/insulin-like growth factor-1 status and response to growth hormone treatment. *Horm Res Paediatr* 2015 **83(1)** 26-35. (<https://doi.org/10.1159/000365507>)

34 Cianfarani S. Safety of Pediatric rhGH Therapy: An Overview and the Need for Long-Term Surveillance. *Front Endocrinol (Lausanne)* 2021 **12** 811-846. (<https://doi.org/10.3389/fendo.2021.811846>)

35 Jorge AAL, Arnhold IJP. Anthropometric evaluation of children with SHOX mutations can be used as indication for genetic studies in children of short stature. *J Med Genet* 2007 **44(10)**e90; author reply e91.

Table Legends

Table 1. Baseline and longitudinal features of total population.

*p <0.05 from longitudinally analysis (T0 - T5) using Friedman ANOVA test

Table 2: Baseline and longitudinal features of study population according to genotype.

*p <0.05 from longitudinally analysis (T0 - T5) using Friedman ANOVA test, in each group.

#p < 0.05 Group A vs. B using Mann-Whitney U test (for numerical variables) and Pearson χ^2 test (for percent values) at the same study time-point.

Table 3. Baseline and longitudinal features of nFH group (n.46).

*p <0.05 from longitudinally analysis (T0 – T4 or T5) using Friedman ANOVA test

Figure Legends

Figure 1. Longitudinal changes in height SDS in total SHOX-D population (χ^2 107.14, p <0.05).

Figure 2. Longitudinal changes in growth velocity (GV) SDS in total SHOX-D population (χ^2 18.27, p 0.002).

Table 1. Baseline and longitudinal features of total population. *p <0.05 from longitudinally analysis (T0 - T5) using Friedman ANOVA test

	T0	T1	T2	T3	T4	T5	X ²	p
Num. pts	117	99	90	72	58	46	n.a.	n.a.
Prepubertal (%)	87/117 (74%)	59/99 (60%)	45/90 (50%)	23/72 (32%)	14/58 (24%)	0/46 (0%)	51.57	<0.05*
Male (%)	61/117 (52%)	51/99 (51%)	45/90 (50%)	39/72 (54%)	30/58 (52%)	19/46 (41%)	1.12	0.95
CA (years)	8.67 ± 3.33	9.68 ± 3.38	10.49 ± 3.33	11.25 ± 3.34	11.92 ± 3.06	15.64 ± 1.49	164.04	<0.05*
BA (years)	7.94 ± 3.15	9.06 ± 3.25	9.85 ± 3.58	10.81 ± 3.98	12.44 ± 3.21	14.97 ± 1.36	23.09	0.00012*
BA delay (years)	- 1.07 ± 1.09	- 0.89 ± 1.10	- 0.77 ± 1.01	- 0.67 ± 1.33	- 0.32 ± 1.19	n.a.	5.82	0.21
H SDS	-2.37 ± 0.67	-1.91 ± 0.64	-1.64 ± 0.73	-1.45 ± 0.62	-1.39 ± 0.64	-1.65 ± 0.94	107.14	<0.05*
BMI SDS	-0.07 ± 0.94	-0.09 ± 0.97	-0.05 ± 1.01	-0.13 ± 0.92	-0.02 ± 0.84	0.28 ± 1.04	13.19	0.02
GV SDS	-1.37 ± 1.65	1.85 ± 2.08	1.32 ± 2.23	0.99 ± 2.02	0.36 ± 2.19	-0.99 ± 2.21	18.27	0.002*
Arm SPAN/H ratio	0.97 ± 0.07	0.98 ± 0.13	0.97 ± 0.03	0.97 ± 0.03	0.97 ± 0.04	0.97 ± 0.02	2.13	0.83
Sitting H/H ratio	0.56 ± 0.02	0.56 ± 0.05	0.55 ± 0.02	0.55 ± 0.01	0.55 ± 0.02	0.56 ± 0.02	19.36	0.0016*
Sitting H/H ratio SDS	2.19 ± 1.27	2.12 ± 1.35	2.10 ± 1.31	2.10 ± 1.28	2.11 ± 1.37	2.24 ± 1.12	9.74	0.08
Rappold's score	7.51 ± 4.86	7.72 ± 5.10	7.14 ± 5.67	7.08 ± 5.41	6.35 ± 5.36	7.57 ± 5.66	1.24	0.94
Tibial Varus (%)	35/101 (34%)	38/69 (55%)	32/79 (40%)	28/65 (43%)	24/50 (48%)	22/42 (52%)	9.12	0.34
Muscular pseudohypertrophy (%)	45/100 (45%)	42/71 (59%)	36/80 (45%)	28/65 (43%)	21/50 (42%)	2/4 (50%)	7.3	0.56
High-arched palate (%)	15/89 (17%)	12/73 (16%)	12/67 (18%)	10/53 (19%)	8/38 (21%)	1/4 (25%)	4.5	0.67
rhGH dose (mg/kg/week)	0.23 ± 0.04	0.24 ± 0.05	0.24 ± 0.06	0.24 ± 0.06	0.24 ± 0.06	n.a.	4.97	0.28
IGF-1 SDS	-0.99 ± 0.93	0.69 ± 1.30	0.87 ± 1.20	0.95 ± 1.42	1.16 ± 1.17	n.a.	48.56	<0.05*

Table 2: Baseline and longitudinal features of study population according to genotype.

*p <0.05 from longitudinally analysis (T0 - T5) using Friedman ANOVA test, in each group.

#p < 0.05 Group A vs. B using Mann-Whitney U test (for numerical variables) and Pearson χ^2 test (for percent values) at the same study time-point.

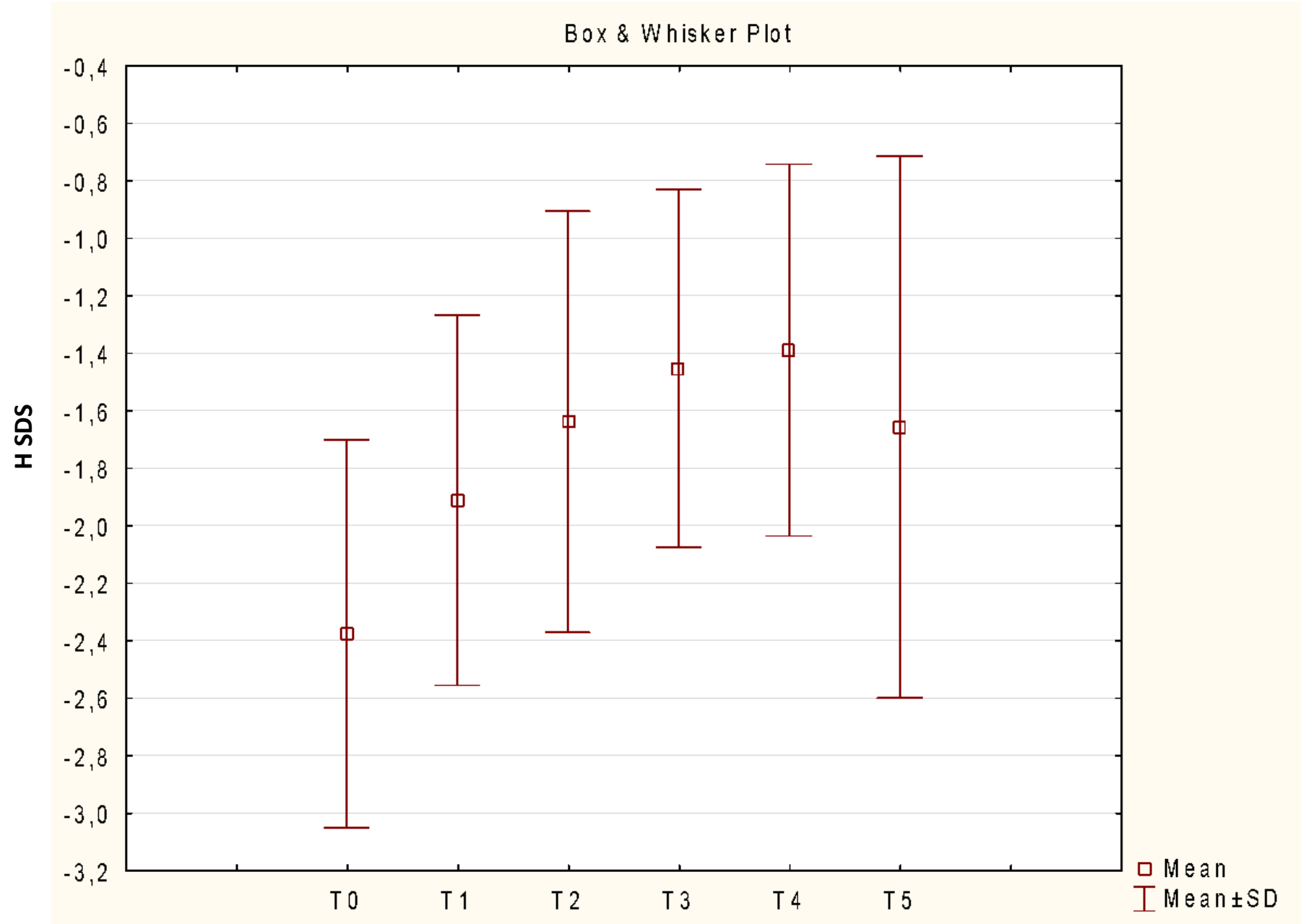
	T0	T1	T2	T3	T4	T5	χ^2	p
Group A: SHOX Intragenic point mutations or deletions (81% prepubertal at diagnosis, 39% reached nFH)								
Num. 75								
CA (years)	8.07±3.34	9.67±3.48	10.68±3.52	11.45±3.52	12.12±3.18	15.79±1.54	94.33	<0.05*
H SDS	-2.34±0.64	-1.87±0.62	-1.50±0.74[#](p0.018)	-1.41±0.66	-1.37±0.69	-1.62±1.00	67.65	<0.05*
BMI SDS	-0.12±0.91	-0.09±0.82	0.03±0.85	-0.04±0.94	0.07±0.89	0.29±0.93	8.42	0.13
GV SDS	-1.28±1.74	2.01±1.98	1.78±2.40[#](p0.014)	1.01±2.08	0.55±2.17	-0.51±2.28	10.76	0.048*
Arm SPAN/H ratio	0.96±0.09	0.98±0.16	0.97±0.02	0.97±0.02	0.96±0.04	0.97±0.02	1.28	0.93
Sitting H/H ratio	0.56±0.02	0.56±0.06	0.54±0.02	0.55±0.01	0.55±0.03	0.56±0.02	9.83	0.07
Sitting H/H ratio SDS	2.29 ± 1.29	2.24 ± 1.43	2.18 ± 1.44	2.25 ± 1.07	2.29 ± 1.12	2.38 ± 1.15	7.29	0.19
Rappold's score	7.87±4.57	8.65±4.68	8.12±5.60	8.33±5.32[#](p0.02)	8.61±5.43[#](p0.01)	8.31±5.33	1.74	0.88
rhGH dose (mg/kg/week)	0.23±0.04	0.24±0.06	0.23±0.06	0.23±0.06	0.23±0.06	n.a.	3.64	0.30
IGF-1 SDS	-1.03±0.88	0.54±1.14	1.07±1.20	1.01±1.42	1.44±1.18[#](p0.03)	n.a.	25.12	<0.05*
Group B: SHOX Enhancers mutations (82% prepubertal at diagnosis, 40% reached nFH)								
Num. 42								
CA (years)	8.56±3.37	9.65±3.30	10.14±3.04	10.83±3.09	11.65±2.94	15.37±1.40	69.72	<0.05*
H SDS	-2.41±0.74	-1.94±0.67	-1.84±0.65[#]	-1.49±0.53	-1.41±0.59	-1.72±0.84	40.57	<0.05*
BMI SDS	0.01±1.01	-0.07±1.20	-0.15±1.25	-0.30±0.88	-0.17±0.76	0.27±1.24	7.41	0.19
GV SDS	-1.57±1.44	1.65±2.25	0.66±1.74[#]	0.87±1.95	0.11±2.23	-1.89±1.93	11.88	0.03*
Arm SPAN/H ratio	0.98±0.03	0.98±0.02	0.98±0.04	0.99±0.03	0.97±0.03	0.97±0.03	4.30	0.50
Sitting H/H ratio	0.56±0.03	0.56±0.02	0.55±0.02	0.55±0.02	0.54±0.01	0.55±0.01	11.79	0.03*
Sitting H/H ratio SDS	2.44 ± 1.26	2.31 ± 1.24	2.30 ± 1.13	2.38 ± 1.19	2.11 ± 1.26	2.46 ± 1.10	2.69	0.74
Rappold's score	6.61±5.02	6.31±5.45	5.96±5.63	4.80±4.46[#]	4.42±4.58[#]	6.56±6.12	1.19	0.94
rhGH dose (mg/kg/week)	0.24±0.05	0.23±0.05	0.25±0.06	0.26±0.05	0.25±0.05	n.a.	11.36	0.009*
IGF-1 SDS	-0.93±1.01	0.92±1.55	0.51±1.15	0.87±1.47	0.76±1.06[#]	n.a.	26.18	<0.05*

Table 3. Baseline and longitudinal features of nFH group (n.46).

*p <0.05 from longitudinally analysis (T0 – T4 or T5) using Friedman ANOVA test

	T0	T1	T2	T3	T4	T5	X²	p
CA (years)	9.67±2.50	10.71±2.55	11.69±2.58	12.26±2.45	13.20±2.38	15.64 ± 1.49	154.04	<0.05*
BA (years)	8.84±2.83	9.94±2.89	11.21±2.81	12.06±2.91	13.30±2.74	14.97 ± 1.36	15.13	0.004*
BA delay (years)	-0.89±1.00	-1.00±1.25	-0.75±0.96	-0.24±1.10	-0.21±1.35	n.a.	3.46	0.48
H SDS	-2.39±0.68	-1.87±0.51	-1.61±0.68	-1.53±0.47	-1.48±0.51	-1.65 ± 0.94	99.77	<0.05*
BMI SDS	-0.13±1.03	-0.19±0.99	-0.13±1.03	-0.16±0.89	-0.11±0.73	0.28 ± 1.04	12.44	0.02*
GV SDS	-1.80±1.47	1.51±1.99	0.82±2.15	0.80±2.09	0.46±2.12	-0.99 ± 2.21	18.27	<0.05*
Arm SPAN/H ratio	0.97±0.03	0.97±0.03	0.96±0.03	0.97±0.02	0.96±0.03	0.97 ± 0.02	2.13	0.83
Sitting H/H ratio	0.56±0.01	0.57±0.07	0.55±0.01	0.55±0.01	0.55±0.02	0.56 ± 0.02	20.18	0.001*
Sitting H/H ratio SDS	2.53 ± 1.06	2.51 ± 0.89	2.31 ± 0.93	2.48 ± 1.01	2.58 ± 1.16	2.24 ± 1.12	11.84	0.036*
Rappold's score	7.19±4.64	7.42±4.85	7.09 ± 5.46	6.70 ± 5.07	6.66±4.95	7.57 ± 5.66	1.25	0.939
rhGH dose (mg/kg/week)	0.25±0.05	0.25±0.05	0.25±0.06	0.26±0.05	0.27±0.05	n.a.	17.74	0.001*
IGF-1 SDS	-0.92±1.09	0.66±1.56	1.05±1.16	0.94±1.49	1.19±1.24	n.a.	22.75	<0.05*

Figure 1. Longitudinal changes in height SDS in total SHOX-D population (χ^2 107.14, $p < 0.05$)



Num. pts	117	99	90	72	58	46

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Figure 2. Longitudinal changes in growth velocity (GV) SDS in total SHOX-D population (χ^2 18.27, p 0.002).

