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# Identification of three novel mutations in 10 pediatric patients with unexplained syndromic short stature identified by targeted exome sequencing in Korea

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## Introduction

- Owing to the tremendous advances in next-generation sequencing technology, numerous monogenic causes of growth disorders have been identified. Identifying novel rare genetic causes of short stature (SS) is quite challenging. In 2017, we reported a mutation analysis of 15 patients with undiagnosed syndromic SS or overgrowth. In this study, 6 mutations in another 10 Korean patients with unexplained syndromic SS are reported.

## Objectives

- The aim of this study was to identify underlying genetic causes of unexplained SS

## Materials and Methods

- Ten pediatric patients with profound SS, mean height of −2.5 SD score (SDS), and a normal growth velocity, some of whom had additional dysmorphic features, were subjected to targeted exome sequencing (TES) study using the Next Seq platform and a TruSight One panel.
- Variants in the dbSNP135 and TIARA databases for Koreans and the variants with minor allele frequencies >0.5% of the 1000 Genomes database were excluded.

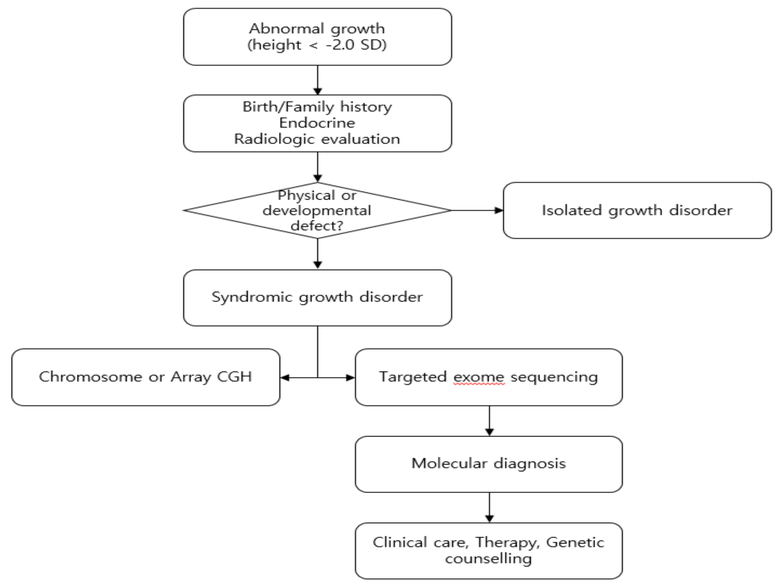


**Figure. Suggested molecular diagnostic algorithms for pediatric patients with short stature**

## Results

Among the 10 patients with unexplained SS, 6 different disorders were identified, and the diagnostic yield was 60%. Most patients confirmed by genetic testing showed distinct facial features, including hypertelorism, low nasal bridge, and abnormal ear shape (Table 1). Most of the cases (4/6, 66.7%) had other accompanying anomalies, including congenital heart disease, kidney anomaly, and skeletal anomaly (Table 1). Two out of the 6 patients (33.3%) were born SGA. Developmental delay or intellectual disability was noted in 3 patients (30%). In the patients with SS, Coffin-Lowry syndrome (CLS) with a novel missense mutation inherited from mother, Cleidocranial dysplasia, Acid-bile subunit deficiency (ALSD) with a novel compound heterozygous mutation, Coffin-Siris syndrome (CSS) with a novel deletion mutation, X-linked creatine transporter deficiency with speech delay, and Acromesomelic dysplasia, Maroteaux type (AMDM) were identified (Table 2).

**Table1. Clinical manifestations in patient with short stature identified by genetic testing**

| Subject | Age at Dx (yrs) | Sex | Ht, cm (SDS) | Wt, kg (SDS) | HC, cm (SDS) | MPH, cm | GA, (weeks) | Birth Wt, kg (SDS) | BA Delay | IGF-I, ng/mL (SDS) | IGFBP3, ng/mL (SDS) | Characteristics |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 9.6 | M | 122.3 (-2.072) | 22.8 (-1.849) | 51.5 (-0.92) | 169.5 | 40+0 | 3.3 (-0.42) | yes | 130.9 (-0.27) | 3790 (0.42) | Hypertelorism, short nose, prominent ear, dolicocephaly, normal intelligence, wormian bone, pseudoepiphysis, delayed teeth eruption, scoliosis |
| 2 | 1.6 | M | 71 (-3.589) | 7.6 (-3.718) | 43 (-3.60) | 170.5 | 39+0 | 2.6 (-1.54) | yes | 41.3 (-0.25) | 1930 (0.11) | Craniofacial features including synophrys, highly arched eyebrows, long eyelashes, and short nose, hirsutism renal stone, global developmental delay, s/p ASD patch closure |
| 3 | 4.8 | M | 48 (-2.873) | 13 (-3.335) | 49.5 (-0.99) | 175.5 | 40+3 | 3.0 (-0.90) | yes | 118.5 (-0.17) | 3600 (0.69) | Subtle facial dysmorphism such as long face and prominent chin, speech and language delay, growth hormone deficiency, DD, autistic spectrum disorder |
| 4 | 7.0 | M | 104.8 (-3.427) | 14.4 (-4.914) | 49 (-2.26) | NA | 39+0 | 3.7 (0.28) | yes | 88.6 (-1.31) | 2280 (-0.09) | Coarse facial appearance, low nasal bridge, broad nose, prominent ear, ADHD, thoracolumbar spondylosis |
| 5 | 12.0 | M | 133.5 (-2.088) | 36.7 (-0.702) | NA | 166.5 | 40+0 | 2.8 (-1.22) | yes | 66.6 (-3.09) | 514 (-0.85) | Subtle dysmorphic face with mandibular hypoplasia and a prominent forehead, SGA, growth hormone deficiency, kyposcoliosis |
| 6 | 1.0 | F | 70 (-2.048) | 8 (-1.340) | 46 (-0.23) | 158.5 | 40+0 | 2.9 (-1.00) | yes | 48.8 (-0.29) | 1930 (0.02) | Relatively macrocephlay with prominent forehead, short arms and legs |

Dx, diagnosis; Ht, height; Wt, weight; HC, head circumference; MPH, mid parental height; GA, gestational age; BA, bone age; SDS, standard deviation score; NA, not available; DD, developmental delay; ASD, atrial septal defect; SGA, small gestational age; NA, not available; yrs, years

**Table2. Genetic results in patients with short stature**

| Subject | Previous clinical assessment | Previous conventional analysis | Final diagnosis | Causative gene | Novelty | cDNA mutations, protein variants | Status, inheritance |
|---|---|---|---|---|---|---|---|
| 1 | Skeletal dysplasia, AD | 46, XY | Cleidocranial dysplasia | *RUNX2* | Reported | c.1171C>T (p.Arg391Ter) | de novo |
| 2 | Cornelia de lange syndrome | *NIPBL* | Coffin-Siris syndrome | *AR1D1B* | Yes | c.5547delC (p.Leu1850*) | de novo |
| 3 | Syndromic disorder | 46,XY | Cerebral creatine deficiency syndrome | *SLC6A8* | Yes | c.942_944del(p.Phe315del) | het, mat |
| 4 | Chromosome disorder | 46,XY | Coffin-Lowry syndrome | *RPS6KA3* | Yes | c.1606G>T(p.Val536Phe) | hemi, mat |
| 5 | Unknown short stature | 46,XY | Acid-labile subunit deficiency | *IGFALS* | Yes | c.1346T>G(p.Leu449Arg) c.1783C>T(p.Arg595Trp) | com het, pat, mat |
| 6 | Achondroplasia | 46,XY, *FGFR3* | Probable acromesomelic dysplasia, Maroteaux type | *NPR2* | Reported | c.2326C>T (p.Arg776Trp) | het, pat |

AD, autosomal dominant; het, heterozygote; mat, maternal origin; pat, paternal origin; hemi, hemizygote

## Conclusions

- TES led to the diagnosis of a monogenic disorder in six of the 10 individuals, including cases with three novel mutations. This study shows that TES is a very promising tool for the identification of pathogenic mutations in patients with unexplained syndromic short stature.

## References

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