Floating-Harbor Syndrome in a Korean Patient with Short Stature and Early Puberty: A Case Report

Jeon J et al. Floating-Harbor Syndrome with Short Stature and Early Puberty

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What is already known on this topic?
FHS is a rare genetic disorder characterized by short stature, language deficits, and distinctive facial appearance. Mutations in the SRCAP gene are responsible.

What this study adds?
This study adds new insights by reporting the first Korean case of FHS with both early puberty and short stature, highlighting the effectiveness of combined human recombinant growth hormone and GnRH agonist therapy for such cases. It emphasizes the significance of genetic testing, particularly SRCAP gene mutation analysis, for accurate FHS diagnosis and contributing to a better understanding of FHS's clinical spectrum and management.

Abstract
Floating-Harbor syndrome (FHS) is a rare autosomal dominant genetic disorder characterized by proportionately short stature, lack of expressive language, and distinctive facial features, including a large nose, long eyelashes, deeply set eyes, and a triangular face. We present a case of an 11-year-old Korean girl who was initially suspected of having Noonan-like syndrome but was later diagnosed with Floating-Harbor syndrome. The patient exhibited short stature, developmental language delay, dysmorphic facial features, and early puberty. Targeted exome sequencing revealed a heterozygous mutation, c.7303C>T (p.Arg2435Ter), in the SRCAP gene, confirming a diagnosis of Floating-Harbor syndrome. She responded well to human recombinant growth hormone and gonadotropin-releasing hormone (GnRH) agonist, effectively suppressing bone maturation and improving her height SDS from -4.6 to -2.4.

Keywords: Floating-Harbor syndrome, Growth Hormone Therapy, Short Stature
height was 131.5 cm (-2.59 SDS), and her weight was 28.4 kg (-2.0 SDS) (Figure 1A). During physical examination, several distinctive features were noted that differed from those of her parents. These included large ears, a short neck, a long nose with a narrow nasal bridge and wide nostrils, mild cubitus valgus, and clinodactyly. Breast development was well suppressed, and bone age was determined to be 11 years, which is six months less than her chronological age. Additionally, there were no anomalies detected in her chemistry or thyroid function tests.

We conducted targeted exome sequencing (TES) to identify the genetic causes of her persistent short stature and facial dysmorphia. DNA samples were obtained from peripheral blood leukocytes using the ChemagCatM Magnetic Separation Module 1 method (PerkinElmer, Chamagen, Baesweiler, Germany) with a DNA Blood 200u kit. The G-Mendelome panel (Celemics, Inc., Seoul, Korea) was used for library preparation, and sequencing was performed using the DNBSQQ-G400 (MGI Tech Co., Ltd., Shenzhen, China), generating 2 × 100 bp paired-end reads. The sequence reads obtained were aligned to the reference sequence based on the public human genome build GRCh37/UCSC hg19 using BWA-mem (version 0.7.17). Duplicate reads were marked with biobambam2, and base quality recalibration and variant calling was performed using the Genome Analysis Toolkit (GATK, version 4.1.8). Annotation was performed using VEP101 (Variant Effect Predictor) and dbNSFP v4.1.

TES revealed a heterozygous variant, NM_006662.3: c.7303C>T, p (Arg2435Ter), in SRCAP (Figure 2). The pathogenicity of this mutation was assessed following the guidelines established by the American College of Genetics and Genomics. Based on the criteria of ACMG/AMP, and PP5, this variant was classified as pathogenic. Additionally, it was not detected in the Genome Aggregation Database (gnomAD).

Consequently, we have determined that it is a pathogenic variant causing a nonsense mutation, leading to the conversion of the arginine residue into a stop codon. These results confirmed the presence of the SRCAP mutation, which ultimately led to a diagnosis of FHS. Notably, no SRCAP variants were identified in the patient’s father, mother, or sister. The patient was maintained on a regimen of 45micrograms/kg/day of rhGH, which had been consistently administered at another hospital. GnRH agonists were discontinued at the age of 12. The patient consulted a doctor for the assessment of hyperopia, strabisimus, and conductive hearing loss, which may be present in FHS. However, the findings of this assessment were unremarkable. The echocardiogram showed favourable result, and renal ultrason showed a difference in size between the two kidneys but no other abnormalities.

The patient is currently 13 years and 4 months old, with a height of 141.9 cm (-2.5 SDS) and a weight of 36.2 kg (-1.8 SDS). She is undergoing rhGH (60 micrograms/kg/day) therapy and receiving continuous speech therapy for delayed language development.

Discussion

In this study, we confirmed the presence of a heterozygous SRCAP variant using TES. The patient exhibited symptoms of short stature, developmental language delay, dysmorphic facial features, and early puberty. FHS can present symptoms resembling those seen in other genetic conditions; therefore, an accurate diagnosis is important. Noonan syndrome, three M syndrome, Rubinstein-Taybi syndrome, and Silver-Russell syndrome must be differentiated from FHS. Noonan syndrome, which shares facial features and short stature with FHS, can be differentiated from FHS by a variety of physical abnormalities, including heart defects. [3, 4] Further, unlike in FHS, patients with Noonan syndrome typically exhibit a large head and normal intelligence and speech development, with the possibility of hypogonadism in affected males. [5] For Rubinstein–Taybi syndrome, patients often display a round face, severe intellectual decline, and normal bone age. [6] In Silver-Russel syndrome, there are different features, such as an asymmetric body, café-au-lait spots, and blue sclera. [7] As these conditions can present symptoms resembling those of FHS, accurate diagnosis and genetic testing by a specialist are necessary.

Only two cases of FHS have been reported in Korea. Both patients had facial dysmorphia and intellectual disabilities, but one patient did not have short stature [1], and the other did not have early puberty [2]. Therefore, our patient was the first in Korea to receive concurrent rhGH therapy and GnRH agonist therapy because of short stature and early puberty.

The pathogenesis of short stature is not completely understood, and it is argued that GH deficiency, GH neurosecretory dysfunction, and IGF-1 signalling defects may be related to FHS, yet the evidence is limited due to the rarity of cases and lack of extensive scientific research. [8] Contrasting with these uncertainties, another study has shown that the effects of rhGH therapy on FHS are modest at best, suggesting that the major molecular pathways of FHS are not caused by reduced GH secretion or activity. [9] This emphasizes the necessity for additional research into the pathogenic mechanisms. In recent literature summarizing the experiences of 22 patients with FHS who received rhGH therapy, no side effects were reported. Notably, except for four individuals, there was a meaningful increase in height SDS compared to before treatment. [4] In our case, the patient received rhGH therapy (45-60micrograms/kg/day) for more than 8 years. The final recorded height of the patient was 147.0 cm (SDS = -2.5), and no adverse effect of rhGH therapy was reported. In our patient, the growth rate improved. Given the rarity of FHS, there is limited information on the outcome of long-term treatment with rhGH. Further studies are necessary to clarify the longitudinal growth pattern and the real effectiveness and safety of rhGH therapy.

Recent studies have suggested potential association between FHS and early puberty. [9] However, the mechanisms underlying early puberty in FHS are poorly understood. Several cases of precocious puberty in FHS patients have been reported, and some patients have undergone treatment with GnRH agonists. [10, 11, 12] Treatment for early puberty in FHS is resembles that for other forms of precocious puberty; however, its effectiveness requires further investigation. Our patient exhibited signs of puberty at the age of 9 years and 10 months. The rapid onset of puberty prompted the initiation of GnRH agonist therapy. This treatment successfully suppressed bone maturation. In FHS patients, early symptoms of short stature and early puberty, we speculate that GnRH agonist therapy could potentially delay bone maturation, thereby extending the duration of rhGH therapy.

At the initial diagnosis of FHS, the growth rate should be evaluated, and renal ultrasonography, blood pressure measurement, ophthalmic examination, hearing testing, dental examination, and genitourinary examination should be performed. [8] For men, it is necessary to check for undescended testes. Orthopaedic examination and evaluation of motor and language development are required for detecting hip dysplasia or other anomalies as well as for genetic counselling. Poor awareness of the disease and the nonspecific clinical symptoms of FHS make its diagnosis difficult and delayed. Patients with short stature, dysmorphic facial features, and developmental delays should undergo genetic investigation, including consideration of conditions such as FHS. In cases like ours, where FHS is accompanied by early puberty and short stature, rhGH therapy and GnRH agonist therapy may be beneficial.

Authors’ Contributions

Conceptualization: Il Tae Hwang. Investigation: Jooyoung Jeon. Writing - original draft: Jooyoung Jeon, Eu-Seon Noh. Writing - review & editing: Il Tae Hwang

Reference

**Figure 1.** (A) Reference growth chart for Korean females (3–18 years)
Heights are marked with red dots, while weights are denoted by green dots. The blue dots represent the bone age. The mid-parental height trend is illustrated by a continuous red line. Significant milestones in the patient's medical treatment are highlighted: the commencement of recombinant human growth hormone therapy is marked by a black arrow, and the initiation of gonadotropin-releasing hormone agonist treatment is indicated by a blue arrow.

(B) Patient's Family Pedigree
The patient highlighted by a black arrow, and the height SDS corresponding to the age of each family member is also displayed

SDS: standard deviation score
Figure 2. Results of Sanger sequencing of the SRCAP gene in the patient NM_006662.3: c.7303C>T, p.(Arg2435Ter), heterozygote, nonsense