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Case Report

A Rare Cause Of Proportional Short Stature and Puberty Precocity: Floating-Harbor Syndrome

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Abstract
Floating-Harbor syndrome is a sporadic autosomal dominantly inherited malformation syndrome characterized by typical craniofacial findings, proportional short stature, significantly delayed bone age, delayed expressive language, delayed speech, and normal head circumference. It is caused by heterozygous mutations in the SNF2-associated CBP activator protein gene (*SRCAP*) located on chromosome 16. Here, we report 9 years and 4 months old male patient who presented to the pediatric genetics outpatient clinic with retardation in early developmental stages, dysmorphic facial features, and short stature. The patient was diagnosed with Floating-Harbor syndrome with typical facial features and clinical findings. A triangular face, short filtrum, posteriorly rotated ear, deep-set eyes, bulbous nose, prominent columella, and low hairline are unique facial features in the syndrome. He also has short stature, significant retardation in bone age, and retardation in expressive language. Floating-Harbor syndrome should be remembered in the differential diagnosis of patients evaluated for short stature and learning disability with its unique facial features. By reporting a new case of Floating-Harbor syndrome we aimed to expand the clinical and molecular spectrum in this rare syndrome and increase diagnostic awareness for pediatric endocrinology practitioners.
Keywords: Floating-Harbor syndrome, *SRCAP* gene, Short stature

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Introduction
Floating-Harbor syndrome (FHS) is a rare hereditary syndrome characterized by a head circumference in the normal range, low birth weight, proportionally short stature, delayed speech, retarded expressive language, and significant retardation in bone age with typical facial features. Floating-Harbor syndrome was first reported in 1973-1974 [1, 2]. The unique facial features of patients may become blurred with age [3]. In addition, microcephaly, trigonocephaly, dental problems, abnormal EEG, late-onset hypertension, cone-shaped epiphysis, and Perthes disease may accompany the syndrome [4]. It occurs due to heterozygous mutations in the SNF2-associated CBP activator protein gene (SRCAP). SRCAP is a 43.2 Kb gene consisting of 34 exons in the 16p11.2 region. It encodes the SNF2-associated CREBBP activator protein. This protein has ATPase activity. It is responsible for cell growth and division by increasing CREB-binding protein (CBP) transcription [5]. Here, a case of Floating-Harbor syndrome who presented to the pediatric genetics outpatient clinic with speech disorder and dysmorphic features and was diagnosed with clinical findings will be reported.

Patient and Methods
A 9-year and 4-month-old male patient was born via cesarean section at 40 weeks of gestation with a birth weight of 3000 grams (-1.2 SDS). He is the fifth child of healthy, non-consanguineous parents. There is no history of special infant care. The patient was referred to the pediatric genetics outpatient clinic due to delays in early developmental milestones, dysmorphic facial features, and short stature. On initial physical examination, the patient's weight was 23 kg (-1.6 SDS), height was 118 cm (-2.66 SDS), body mass index (BMI) was 0.01 SDS, arm span was 111 cm, and head circumference was 52 cm (-0.81 SDS). The pubertal examination was normal, with Tanner stage 1, but bone age was approximately 4 years as assessed by X-ray (Figure 1d). The dysmorphic evaluation revealed a triangular face, deep-set eyes, prominent nasal root, low-set ears, bulbous nose, low-hanging columella, and short philtrum (Figure 1, a-b-c). Developmentally, the patient began walking at 1.5 years of age and talking at 3 years of age. He exhibited significant expressive language delays and shy behavior. Initial hematologic, biochemical, and metabolic parameters were within normal limits. At 10 years and 3 months of age, the patient was evaluated by the pediatric endocrinology department due to short stature and early puberty. Physical examination revealed a weight of 28.8 kg (-0.86 SDS), height of 126.8 cm (-1.9 SDS), BMI of 0.66 SDS, and arm span of 124 cm. Annual growth was 8.8 cm, with an increase in height velocity. Bone age was 6 years (Figure 1, e), showing a 2-year increase within 1 year. Testicular volume was 8-10 cc, appropriate for his age. Endocrinological evaluation showed follicle-stimulating hormone (FSH) level of 2.2 U/L (reference range: 0.3-10.1), luteinizing hormone (LH) level of 2.2 U/L (reference range: <6), and testosterone level of 1.02 µg/L. Insulin-like growth factor 1 (IGF1) level was 157 µg/L (reference range: 63-271), and insulin-like growth factor binding protein 3 (IGFBP3) level was 7.6 (reference range: 2.4-8.4), both within normal ranges. Pituitary and brain magnetic resonance imaging (MRI) were normal, and follow-up was conducted for early and rapid puberty. Echocardiography and abdominal ultrasound screening showed no major organ abnormalities. Hearing test results were normal, and the ophthalmology department followed the patient for esotropia with corrective glasses. Psychometric evaluation using the Wechsler Intelligence Scale for Children (WISC-R) identified mild to moderate intellectual disability. The patient is receiving special education for cognitive and speech delays.

Karyotype analysis revealed a normal 46 XY result. Microarray analysis showed no pathogenic copy number variations (Illumina Infinium CytoSNP 850K). Fragile X gene DNA analysis with triplet primer Polymerase Chain Reaction (PCR) identified 56 CGG repeats, placing the patient in the Fragile X premutation range. Due to the clinical presentation and dysmorphic features suggestive of Floating-Harbor syndrome, sequencing of the SRCAP gene was performed. Next Generation Sequencing (NGS) of the SRCAP gene revealed a heterozygous c.7330C>T p.(Arg2444Ter) variant in exon 34, which causes premature termination. This variant is classified as pathogenic according to ACMG criteria. Verification with Sanger sequencing confirmed the presence of this variant in the patient in the heterozygous state. This variant was not detected in the Sanger sequencing of the parents, thus it is interpreted as disease-causing *de novo*.

Discussion
Floating-Harbor syndrome is a very rare malformation syndrome with autosomal dominant inheritance characterized by short stature, typical facial features, and significant delay in bone age [1]. A total of 100 cases of this extremely rare syndrome have been reported [6]. It occurs with mutations in the *SRCAP* (SNF2-related CREB associate protein) gene located on chromosome 16. The *SRCAP* gene encodes the SNF2-related CREB binding protein. This protein has a role in the activation of the *CREBBP* (CREB binding protein) gene, which is involved in

the exchange of histone dimers in the nucleosome and provides transcriptional regulation by remodeling chromatin. CREB binding protein, the protein encoded by the *CREBBP* gene, is involved in cell proliferation and normal growth [7, 8]. The mutations reported so far are especially clustered in the 34th exon and the variant in our patient was also located in the 34th exon [9]. There is no known genotype-phenotype relationship in the reported cases. In the series of 13 cases reported by Hood RL. et al. 6 patients had the same variant that was also found in our patient. Facial-specific features are the most important differential diagnostic step in Floating-Harbor syndrome [10]. Our patient had the specific facial features of the syndrome with a triangular face, prominent nasal root, inferiorly located columella, thin upper lip vermillion, and deeply located eye findings. Low birth weight can be seen in Floating-Harbor syndrome however it is not characteristic of this syndrome. Our patient was born at 40 weeks with a birth weight of 3000 g (-1.48 SDS). The patient had a normal birth weight according to anthropometric measurements at birth. Thirteen out of 49 patients were reported to have a birth weight below -2 SDS in the literature [9]. Short stature is the cardinal sign of FHS, and may occur in a variable range in patients with Floating-Harbor syndrome. The exact mechanism by which *SRCAP* mutations cause a short stature has not been fully elucidated. It is thought that anomalies that cause irregularity in chondrocyte proliferation and maturation may affect the growth phenotype of patients with FHS by causing a delay in long-bone development [11]. It has also been reported that short stature may be associated with Growth Hormone (GH) deficiency, GH neurosecretory dysfunction, and IGF-1 signaling defects [12]. In a series of 52 patients reported from two previous studies, the maximum height in girls was 20 percentile and the majority of the cases were located between -2 and -4 SDS. In boys, the maximum height was 25 percentile and 2 adults were -4 SDS [9]. In another study, the heights of 13 patients ranged between -4.3 SDS and -0.6 SDS [13]. When the growth parameters of previously reported patients were analyzed, it was reported that head circumference for height was within the normal range [9]. Similarly, the presented patient's height was -2.2 SDS and head circumference was 0.81 SDS in the normal range. Growth hormone may be one of the treatment alternatives in Floating-Harbor syndrome [14, 15]. In a study evaluating 22 cases receiving GH treatment most of whom showed accelerated growth and improved height SDS [12]. However, as the IGF-1 level of our patient fell within the normal range for his age, growth hormone treatment was not considered. He is being monitored for potential growth hormone therapy based on an ongoing assessment of his growth rate.

Significant delay in bone age, which is one of the essential features of FloatingHarbor syndrome, was reported in all patients in a series of 13 cases. Although there is a significant delay in bone age (≥2 SD below the mean), normalization in bone age is expected between the ages of six and 12 years. The calendar age of our patient was 9 years and 4 months and the bone age was 3 years and 6 months [13]. Interestingly, in the follow-up, a 3-year improvement in bone age was detected in 1 year. This situation may also be due to our patient's fast puberty. Puberty precocity is among the features reported in patients with Floating-Harbor syndrome and the underlying mechanism is still unknown. [14]. In the literature, cases have been reported in which GnRH analog treatment was started due to early puberty, and bone maturation was successfully suppressed [16]. In the case of Stagi et al., it was reported that adult height of -1.2 sds was achieved with both GH and GnRHa treatments. In the presented case, an early and fast puberty was detected and GNRHa treatment will be planned according to the follow-up.

Expressive language delay is one of the major findings of the syndrome and our patient was receiving speech therapy due to significant delay in expressive language [10]. In one study, the frequency of attention deficit hyperactivity disorder was reported to be 28% and in another study, the frequency of behavioral problems was reported to be 60%; our patient was being treated for attention deficit hyperactivity disorder but had no behavioral problems [7, 9, 13, 14]. In our patient, premutation was detected with 54 repeats in the CGG 3-repeat analysis for Fragile X syndrome, but we diagnosed FloatingHarbor syndrome with further molecular analysis because of dysmorphic facial finding and short stature. The patient being a Fragile X premutation carrier could potentially affect their behavioral phenotype and intellectual disability profile. In a study of 52 cases, although at least one major organ anomaly was found in 33 of the patients diagnosed with Harbor syndrome, no specific anomaly was reported for Floating-Harbor syndrome, and our patient had no major organ anomaly [9].

Floating-Harbor syndrome must be distinguished from other genetic conditions with short stature. Rubinstein-Taybi syndrome was ruled out due to the absence of its characteristic features and organ anomalies. Silver-Russell syndrome was unlikely because the patient's head circumference and birth weight were normal. 3M syndrome was excluded as the patient did not have the typical skeletal features and had developmental delays. The SHORT syndrome was not considered due to the lack of associated symptoms such as hearing loss and joint laxity. Aarskog syndrome was also excluded because the patient's facial features did not match those of the syndrome.

Floating Harbor syndrome should be considered in the differential diagnosis in patients investigated for short stature and learning disability with specific facial features. Although our patient was found to be a premutation carrier in Fragyl X analysis carried out for a learning disability, he was diagnosed with Floating Harbor Syndrome with a molecular examination performed because of his unique facial findings. In this article, we report a new case of Floating Harbor syndrome which was diagnosed and evaluated because of short stature, precocious puberty, and dysmorphic facial features. We aimed to expand the clinical spectrum in patients with short stature, precocious puberty, severe bone age retardation, and dysmorphic facial features and to increase the awareness of rare genetic diseases in pediatric endocrinology practitioners.

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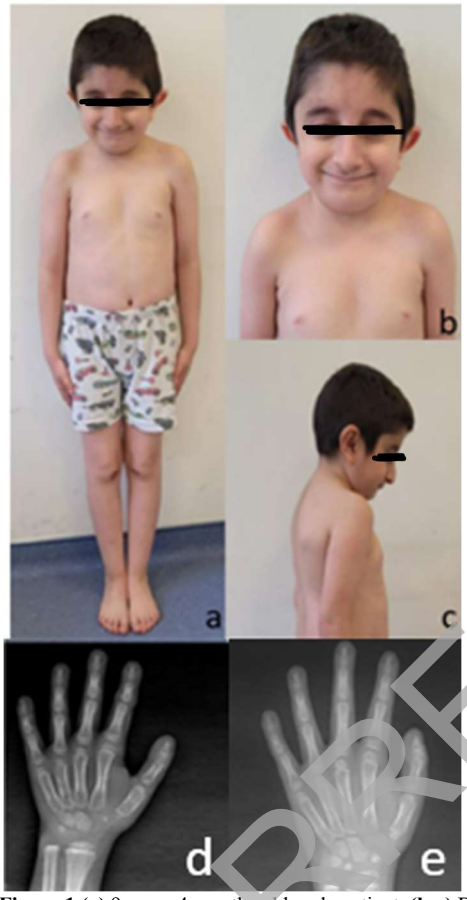

Figure 1 (a) 9 years 4 months old male patient, **(b-c)** Dysmorphologic evaluation triangular face, deep-set eyes, , low-set ear, bulbous nose, low hanging columella, short filtrum **(d)** Bone age consistent with 3 years 6 months **(e)** Bone age consistent with 6 years