

Autism Spectrum Disorder in a Child with Floating-Harbor Syndrome: A Case Report

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ABSTRACT

Introduction: The genetic basis of autism spectrum disorder (ASD) is highly heterogeneous and continues to be elucidated through syndromic associations. Floating-Harbor Syndrome (FHS) is a rare genetic disorder caused by SRCAP mutations and is characterized by short stature, expressive language delays, and distinct craniofacial features. This report aims to present the diagnostic process and clinical challenges of a child diagnosed with both FHS and ASD.

Case: A 9-year-old boy presented with social communication difficulties, restricted interests, and sensory hypersensitivity. Psychometric testing demonstrated average intellectual functioning (IQ: 94), while behavioral assessments revealed significant hyperactivity and behavioral dysregulation, in addition to severe autism as measured by the Childhood Autism Rating Scale (CARS). Based on DSM-5 criteria, he was diagnosed

with ASD. Persistently elevated amylase and lipase levels prompted genetic evaluation, which confirmed FHS with an SRCAP mutation.

Discussion: This case underscores the diagnostic challenges of differentiating syndrome-specific features from true comorbid ASD when overlapping symptoms such as language delay and behavioral problems are present. These findings highlight the importance of comprehensive psychiatric and genetic evaluation in children with complex developmental profiles, and highlights the need for systematic screening for neurodevelopmental disorders in rare genetic syndromes.

Keywords: Autism Spectrum Disorder, case report, comorbidity, Floating-Harbor Syndrome

Cite this article as: Kaan H ve Coskun M. Autism Spectrum Disorder in a Child with Floating-Harbor Syndrome: A Case Report. Arch Neuropsychiatry 2026;63:299–301. doi: 10.29399/npa.29177

INTRODUCTION

Examining autism spectrum disorder (ASD) within the context of specific genetic syndromes provides critical insights into its pathogenesis and may help differentiate syndrome-specific phenotypic presentations. In recent years, attention has been given to even rarer genetic syndromes that may also present with ASD features (1–4)

Floating-Harbor syndrome (FHS) is a rare genetic disorder caused by mutations in the SRCAP (Snf2-related CREBBP activator protein) gene, which plays a key role in chromatin remodeling and transcriptional regulation (5). Since its first description in 1973, more than 100 cases of FHS have been documented worldwide (6). FHS is clinically characterized by short stature with delayed bone age, expressive language deficits, and distinct craniofacial appearance, often involving a triangular face (5). Additional features such as hearing loss, skeletal abnormalities, congenital heart defects, and hydronephrosis have also been reported. Neurodevelopmental challenges, including learning difficulties and intellectual disabilities, are frequently reported; however, the association between FHS and ASD remains poorly understood (7).

Highlights

- This case contributes to the limited literature on the co-occurrence of FHS and ASD.
- A de novo SRCAP variant highlights the complex genetic basis of ASD.
- This case shows the need for detailed genetic evaluations in atypical ASD cases.

Although ASD has been increasingly recognized in association with various genetic syndromes, documentation of its coexistence with FHS remains scarce. In this case report, we present a child diagnosed with both FHS and ASD, aiming to contribute to the limited literature on this rare comorbidity.

CASE REPORT

A 9-year-old boy presented to the child and adolescent psychiatry outpatient clinic with primary complaints of sensory hypersensitivity and difficulties in social interaction. Clinical history revealed that the child had difficulty maintaining relationships, exhibited an unusual fascination with smells, and frequently used idiosyncratic language. Additional information obtained during the assessment indicated persistent ritualistic behaviors, distress when routines were disrupted, and an intense preoccupation with specific topics, particularly letters and symbols. Reports from teachers were consistent with these findings, noting persistent difficulties in forming peer relationships, heightened reactivity to auditory stimuli, and frequent self-directed speech during class activities. Teachers also described low frustration tolerance, emotional immaturity, and episodes of behavioral dysregulation. During the clinical interview the child displayed limited eye contact, grimacing facial expressions, and frequent self-directed speech. Developmental history revealed a delay in expressive language development. There was no known family history of neurodevelopmental or psychiatric disorders, and no parental consanguinity was reported. On physical examination, the patient's height and weight were both below the 5th percentile (height: 120 cm, weight: 21 kg). Previous endocrinological evaluation had revealed a bone age delay of approximately four years, although growth hormone levels were within normal limits. Psychometric testing and clinical observation as part of the neurodevelopmental assessment revealed average intellectual functioning, with an IQ score of 94 on the Wechsler Intelligence Scale for Children-Revised (WISC-R). The Conners Teacher Rating Scale was administered to assess behavioural and attentional functioning. The results indicated significant elevations in the hyperactivity subscale (score: 14) and the behavioural problems subscale (score: 16). These results, together with clinical observations and parental interviews, supported a diagnosis of ASD according to DSM-5 criteria. To evaluate autism severity, a comprehensive psychiatric assessment was carried out, including the Childhood Autism Rating Scale (CARS), which yielded a total score of 39, indicating the 'severe autism' category. The patient was subsequently referred for personalised educational planning, with a particular focus on structured behavioural interventions and sensory integration therapy.

During follow-up, the patient exhibited increased behavioral rigidity, intensified repetitive behaviors, and emotional outbursts, particularly within the school setting. Due to the worsening of these symptoms and their impact on daily functioning, pharmacological treatment was initiated with low-dose aripiprazole (1 mg/day) and escitalopram (0.5-1 mg/day). Routine laboratory tests conducted for medication monitoring revealed significantly elevated serum amylase and lipase levels. Despite discontinuation of both medications, the enzyme elevations persisted. Subsequent gastroenterological assessments, including imaging and metabolic panels, showed no structural or functional abnormalities in the pancreas or hepatobiliary system.

Given the diagnosis of ASD, along with growth retardation and persistent biochemical abnormalities, the patient was referred for further evaluation. Chromosomal microarray analysis and whole exome sequencing, performed as part of this assessment, revealed a *de novo* truncating pathogenic variant in the SRCAP gene, confirming a diagnosis of Floating-Harbor Syndrome (FHS). Additional syndromic features included a spontaneously regressed atrial septal defect diagnosed in early childhood, hirsutism (notably long eyelashes requiring trimming), dental fragility despite routine oral care, and distinct craniofacial dysmorphism, including a triangular-shaped face and a thin vermilion border of the upper lip. Written informed consent for the publication of anonymised clinical information for this case report was provided by the patient and his parents.

DISCUSSION

This case report presents a rare instance of co-occurrence of FHS and ASD, contributing to the expanding body of literature on ASD in the context of genetic syndromes (8). While children with FHS frequently exhibit mild-to-moderate intellectual disability, language delays, and sometimes ADHD-like features, reports specifically addressing ASD in the context of FHS remain scarce (7). This case highlights the importance of genetic evaluations in children diagnosed with ASD, particularly when additional clinical features suggest an underlying syndromic disorder.

FHS is caused by pathogenic variants in the SRCAP gene, which encodes a key protein involved in chromatin remodeling and transcriptional regulation (5). Given the critical role of chromatin modification in brain development and synaptic plasticity, disruptions in these processes have been implicated in a range of neurodevelopmental disorders (9). Related conditions, such as CHD8- and KMT2A-associated syndromes, also exhibit strong links to ASD, further supporting the role of epigenetic regulation in ASD pathogenesis (10). Additionally, Rubinstein-Taybi Syndrome (RTS), caused by mutations in CREBBP—a coactivator of SRCAP—shares several clinical features with FHS and has been associated with ASD-like behaviours (11). The SRCAP gene is categorized as "Score 1 (High Confidence)" in the SFARI (Simons Foundation Autism Research Initiative) Gene database, indicating that there is strong, replicated evidence linking SRCAP mutations to autism spectrum disorder, independent of its syndromic association with FHS. Recent animal studies have provided further support for this hypothesis. A study involving *Srcap*^{-/-} mice demonstrated that SRCAP haploinsufficiency leads to neurodevelopmental disorders, including social interaction deficits, repetitive behaviours, and impaired learning (12). The clinical spectrum of SRCAP-related disorders has broadened with reports indicating that truncating variants outside the classic FHS locus can produce distinct neurodevelopmental phenotypes, characterised by developmental delay, intellectual disability, behavioural problems, and psychiatric symptoms, including ASD (13). Taken together, these findings imply that SRCAP mutations may be associated with a clinical spectrum of neurodevelopmental outcomes.

Despite the distinctive craniofacial characteristics associated with FHS, clinical recognition can be challenging, with diagnoses often made around seven to eight years of age (6). This suggests that the hallmark physical findings may not be sufficient for early clinical suspicion. In this patient, an ASD diagnosis was initially made, prompted by prominent social-communication deficits and repetitive behaviours. However, persistently elevated amylase and lipase levels prompted a more thorough investigation, leading to the diagnosis of Floating-Harbor syndrome (FHS). This diagnostic approach highlights an important bidirectional clinical principle: a diagnosis of ASD in the context of atypical developmental features should prompt consideration of an underlying genetic cause. The reverse is also crucial – children diagnosed with rare genetic syndromes such as FHS should undergo systematic screening for neurodevelopmental disorders, including ASD. This is particularly important when behavioural manifestations are more severe or qualitatively different to those typically associated with the genetic condition alone. In this case, distinguishing between symptoms attributable to FHS and ASD presented a significant clinical challenge due to the presence of overlapping features, such as expressive language delay and behavioural dysregulation. This diagnostic complexity is not unique to FHS, as it has also been reported in other genetic syndromes frequently associated with ASD, including Fragile X syndrome, tuberous sclerosis complex and Rett syndrome, where overlapping symptoms can obscure or delay recognition of comorbid autism (14). A critical clinical

marker in distinguishing a true ASD diagnosis from syndrome-specific manifestations is the presence of more severe deficits or qualitatively distinct deficits in social communication and restrictive, repetitive behaviours than would be anticipated from the primary genetic disorder or general cognitive delay alone. This patient met all the criteria in the DSM-5 for an ASD diagnosis, including persistent deficits in social reciprocity, fixed and restricted interests, insistence on sameness and heightened sensory reactivity. These findings support the interpretation that the patient's ASD represents a distinct co-occurring condition rather than a misattribution or exaggeration of the FHS phenotype. This highlights the importance of comprehensive, multidisciplinary evaluations incorporating genetic, developmental and behavioural assessments when atypical neurodevelopmental features are observed in children with syndromic presentations.

Furthermore, given the high prevalence of psychiatric comorbidities in ASD, pharmacological intervention is frequently required (15). However, in the presence of an undiagnosed genetic syndrome, unexpected drug responses and adverse effects may occur (1). In this case, the patient had persistently elevated amylase and lipase levels, raising concerns about possible subclinical pancreatic involvement. While pancreatic enzyme elevations have not been commonly associated with FHS, previous research suggests that individuals with chromatin remodeling disorders may exhibit metabolic and gastrointestinal abnormalities (7). The patient had been administered Aripiprazole and Escitalopram, both of which have been associated with rare instances of drug-induced pancreatitis (16). However, despite the discontinuation of these medications, amylase and lipase levels remained elevated, indicating the presence of an alternative underlying mechanism. This persistent elevation in enzyme levels suggests the possibility of an as yet unexplored metabolic component in FHS or a complex interaction between genetic factors and neuropsychiatric medication use.

This case underscores the importance of genetic evaluations in atypical ASD cases, particularly when additional clinical features suggest an underlying syndromic disorder that may influence presentation and management. Given the genetic heterogeneity of ASD and its association with multiple monogenic disorders, studying cases like this may provide insights into the broader mechanisms underlying ASD (14). Although the observed symptom overlap between FHS and ASD may suggest a shared etiological pathway—and considering that SRCAP is listed as one of the genes associated with ASD, the rarity of ASD and FHS comorbidity raises the possibility that their co-occurrence in this case may be coincidental rather than causally related. Further research, including detailed genetic analyses and longitudinal follow-up of individuals with FHS, is essential to determine the true prevalence of ASD in this population and to clarify the neurobiological pathways through which SRCAP dysfunction may contribute to autism-related phenotypes.

In conclusion, this case demonstrates the necessity of genetic evaluations in ASD, particularly when confronted with atypical or complex clinical presentations. The identification of a hidden genetic disorder can significantly impact diagnostic accuracy, treatment decisions, and long-term management strategies. Further research investigating the neurogenetic basis of FHS and its potential overlap with ASD may provide valuable insights into the pathophysiology of both conditions.

Informed Consent: Written informed consent for publication of anonymized clinical information was obtained from the patient and family.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- HK, MC; Design- HK, MC; Supervision- MC; Materials- MC; Data Collection and/or Processing- MC; Analysis and/or Interpretation- HK, MC; Literature Search- HK, MC; Writing- HK, MC; Critical Reviews- MC.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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