

Case Report

Thauvin-Robinet-Faivre Syndrome: A *FIBP* Variant in an Adolescent with Segmental Overgrowth and Thyroid Carcinoma

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What is already known on this topic?

Overgrowth syndromes are rare diseases seen in pediatric endocrinology clinics. Those affecting growth factor pathways may present with body parts or limb hypertrophy and a predisposition to malignancy, including endocrine organs. FGF-1 intracellular binding protein (*FIBP*) gene variants cause Thauvin-Robinet-Faivre Syndrome, a new disease defined in this pathway.

What does this study adds?

Our case represents the ninth case reported worldwide and the fifth from Turkey, contributing to the literature in terms of clinical findings and clinical presentations in cases with suspected tumor predisposition.

Abstract

Overgrowth syndromes are rare genetic disorders arising from alterations in the growth factors pathway. These syndromes can present as generalized overgrowth, characterized by macrosomia and excessive height compared to peers, or partial overgrowth syndromes, where specific body regions exhibit disproportionate growth often accompanied by vascular anomalies. Both forms are associated with an increased risk of tumor development. The FGF-1 intracellular binding protein (*FIBP*) gene plays a critical role in cell proliferation and differentiation by interacting with growth factors. In this article, we present a case of Thauvin-Robinet-Faivre Syndrome (TROFAS) in a 16-year-old girl, diagnosed with homozygous NM_004214.5 c.412-3_415dup (p.Asp139AlafsTer3) variant in the *FIBP* gene. This case exhibits phenotypic features and tumor development, including thyroid follicular carcinoma and parotid mucoepidermoid carcinoma, that have not been previously reported in association with this syndrome. Recent studies have implicated *FIBP* gene defects in overgrowth syndromes, with only a limited number of cases described globally. Our case expands the known clinical and tumor spectrum associated with TROFAS, providing new insights into the pathophysiology of this rare disorder.

Keywords: Overgrowth Syndromes, FGF-1 intracellular binding protein (*FIBP*) gene, Cancer

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Introduction

Overgrowth syndromes comprise a diverse group of disorders characterized by prenatal overgrowth, persistent postnatal overgrowth in both weight and height, segmental overgrowth, congenital malformations, intellectual disability, and, in some cases, an increased risk of neoplasia. Segmental overgrowth refers to excessive growth localized to specific body regions, such as a single digit, an extremity, one side of the face, or the head (macrocephaly). It often presents asymmetrical overgrowth of musculoskeletal, adipose, or brain tissue, vascular malformations and overlying skin lesions. This phenotype is frequently associated with mosaic variants in the phosphoinositide-3-kinase-protein kinase B (PI3K/AKT)/mammalian target of rapamycin (mTOR) pathway, a key signaling cascade activated by growth factors such as insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) (1–3).

The FGF-1 intracellular binding protein (*FIBP*) gene, located on chromosome 11q13.1, is expressed in the membranes of microsomes and mitochondria within the cytoplasm and nucleus (4). The interaction between fibroblast growth factors (FGFs) and their receptors (FGFRs) plays a crucial role in multiple biological processes, including embryogenesis, neuronal development, and the formation of bone, cartilage, and vascular structures (4,5).

Thauvin-Robinet-Faivre Syndrome (TROFAS) is a rare autosomal recessive disorder caused by biallelic pathogenic variants in the *FIBP* gene. TROFAS (OMIM: 617107) is characterized by a broad spectrum of phenotypic features, including mild to severe learning difficulties, distinctive facial dysmorphisms, enlarged hands and feet, generalized overgrowth, and a predisposition to various congenital anomalies affecting the heart, eyes, kidneys, and skeleton. Only eight cases of TROFAS have been reported worldwide, making it a largely under-recognized condition with limited available literature (6–9).

Here, we present the case of a 16-year-old female patient diagnosed with a homozygous likely pathogenic variant in the *FIBP* gene, born to consanguineous parents. This case is particularly notable due to the malignancies and distinct clinical features not previously described in other reported TROFAS cases.

Case Description

A 16-year-old female presented with a six-month history of swelling on the right side of her neck and chin. She had previously undergone surgery at another hospital, where a right hemithyroidectomy and excision of a right parotid mass were performed. Histopathological examination revealed thyroid follicular carcinoma and a low-grade mucoepidermoid carcinoma of the parotid gland.

The patient was born at full term to consanguineous parents, with a birth weight of 2800 g. Her neuromotor developmental history was notable for significant delays; she began walking at the age of 3 years and started speaking between 6 and 7 years of age. The family history included two healthy siblings, one sister with congenital heart disease, and two siblings who died in the neonatal period for unknown reasons.

On physical examination, her weight was 59.6 kg (66th percentile), height was 159.3 cm (29th percentile), and body mass index (BMI) was 23.5 kg/m² (79th percentile). Her head circumference measured 56.8 cm (77th percentile). Sitting height was 85 cm, with a sitting height-to-height ratio of 0.53 (within the normal range). Her arm span was 163 cm, with an arm span-height difference of 4 cm (+1 SD to +2 SD). Pubertal assessment was consistent with Tanner stage 5; she had menarche at 12.5 years, and her menstrual cycles were regular.

Notable facial features included a flat midface, mild right ptosis, low palpebral fissures, deep-set eyes, thick lips, thick and broad eyebrows with mild synophrys, a pointed chin, a prominent nasal bridge, a narrow forehead, a high palate, posteriorly rotated ears, and raised earlobes. Skeletal examination revealed mild pectus excavatum and pes planus. Additionally, she had enlarged hands and feet, broad port-wine stains on her arms and legs, and varicose veins in both legs. Syndactyly was present between the second and third toes on the left foot, and a flexion contracture was noted between the first and second phalanges of the third finger on the right hand, which developed following hemangioma surgery (Figure 1, Figure 2). Numerous nevi were also observed on her face and trunk. The patient had an intellectual disability.

Parental heights were 155 cm (-3.4 SD) for the father and 157 cm (-1.04 SD) for the mother. Her 25-year-old brother's height was 169 cm (-1.17 SD), and her 20-year-old sister's was 158 cm (-0.87 SD). It was reported that her 14-year-old sister has a normal height but is being followed at another center for a cardiac condition.

Laboratory tests, including a complete blood count and biochemistry, were unremarkable. Eye and hearing examinations were normal; her IQ score was 65. Radiographic imaging showed mild thoracic scoliosis and closed epiphyses. Abdominal and renal ultrasonography did not detect any anomaly. Anatomical variation was noted, with the hepatic artery originating directly from the abdominal aorta, while the splenic and left gastric arteries arose from a single branch. Venous Doppler imaging revealed multiple enlarged perforating veins with reflux, connected to the great saphenous vein, with numerous varicose veins in both legs. An echocardiogram detected mild mitral valve prolapse, trace mitral regurgitation, and a small atrial septal defect.

Surgery and pathology reports indicate that the 3x2.5 cm diameter nodule removed from the right lobe hemithyroidectomy material is non-invasive follicular carcinoma, and the 3.5x3 cm mass removed from the right parotid is low-grade mucoepidermoid carcinoma. No metastatic or residual mass was detected in further scans.

Method and Result

We performed whole exome sequencing (WES) for the patient and her healthy father using the Illumina DNA Prep & TWIST Bioscience Exome 2.0 Plus Comprehensive Exome library preparation and the Illumina NovaSeq 6000 sequencing platform. The bioinformatics analysis pipeline included the Burrows-Wheeler Aligner (BWA 0.7.15) for read alignment, the Genome Analysis Toolkit (GATK 3.6) for variant calling, and the Variant Effect Predictor (VEP 89) for annotation. Variants were filtered based on their frequency using public and in-house databases (e.g., gnomAD).

Variant pathogenicity was assessed according to the 2015 ACMG (American College of Medical Genetics and Genomics) guidelines. Variants in the *FIBP* gene that met the analysis criteria, correlated with the clinical phenotype, and had variant allele frequency (VAF) values consistent with the expected inheritance pattern were reported. Whole exome sequencing revealed a c.412-3_415dup p.Asp139AlafsTer3 frameshift homozygous likely pathogenic variant in the *FIBP* gene (NM_004214.5), classified according to ACMG criteria as PVS1-PM2. Family segregation analysis confirmed that the father was a heterozygous carrier of this variant, but maternal carrier status could not be verified due to the lack of available DNA samples. The *FIBP* gene is known to follow a loss-of-function disease mechanism, and the identified variant was absent in population databases, including gnomAD, ExAC, and the Turkish Variome.

Discussion

Fibroblast growth factor 1 intracellular binding protein is a protein that binds acidic fibroblast growth factor (aFGF) intracellularly, leading to morphological changes, differentiation, and stimulation of mitogenic activity in various cell types (4).

The fibroblast growth factor receptor (FGFR) family, similar to insulin-like growth factor (IGF) receptors, functions through tyrosine kinase signaling pathways. Activation of FGFRs initiates downstream signaling cascades, including the MAPK and PI3K/AKT pathways, which play crucial roles in cellular differentiation, proliferation, survival, and migration. These pathways are also involved in angiogenesis, vascular repair, and wound healing. Aberrations in FGFR genes such as translocations, amplifications, or activating variants have been implicated in various malignancies, including gastric, lung, breast, and ovarian cancers (10).

Thauvin-Robinet et al. first described TROFAS in 2016 in a 23-year-old male of North African descent, born to consanguineous parents. The patient exhibited overgrowth, macrocephaly, intellectual disability, facial dysmorphism, bilateral retinal coloboma, ventricular septal defect, mitral valve prolapse, bifid ureter, renal malrotation, transient neutropenia, and varicose venous anomalies. The biallelic variant identified in the *FIBP* gene suggested that loss of function in the intracellular domain of FGF receptors may be associated with overgrowth syndromes. Further analysis of the patient's fibroblasts demonstrated significantly reduced *FIBP* cDNA expression but an increased proliferation rate compared to controls, indicating a potential link between *FIBP* dysfunction and overgrowth via the FGFR3 pathway (11, 12).

In 2016, a homozygous indel variant (NM_198897.1 c.175_176insTAA, p.His59delinsLeuAsn) was identified in three siblings from an Arab family, each presenting with an overgrowth syndrome accompanied by congenital abnormalities. Functional studies using in vitro and in vivo models demonstrated that patient derived fibroblasts exhibited markedly increased proliferation rates, reinforcing the association of *FIBP* loss-of-function variants with human overgrowth syndromes (13).

A recent case from Turkey described a 9-year-old boy with distinct dysmorphic features, including macrosomia at birth, neuromotor delay, and intellectual disability. His facial features included a triangular face, midface retrusion, pointed chin, deep-set eyes, hypertelorism, long and wavy palpebral fissures, a prominent nasal bridge, thick and broad eyebrows with mild synophrys, a short philtrum, a high palate, and posteriorly rotated ears with upturned earlobes. Additional findings included chest narrowing, mild pectus excavatum, hyperextensible elbow joints, pes planus, telangiectasias, hypoplastic nipples, and unilateral cryptorchidism. Genetic analysis via exome sequencing identified a homozygous frameshift variant (NM_004214.5 c.412-3_415dup, p.Asp139AlafsTer3) in the *FIBP* gene, which was classified as likely pathogenic (6). Subsequently,

three additional cases with a similar phenotype carrying the same homozygous NM_004214.5 c.412-3_415dup, p.Asp139AlafsTer3 variant were reported from Turkey. All reported cases' clinical and genetic characteristics are summarized in Table 1 (6-9).

The same frameshift variant was also detected in our patient, introducing a premature stop codon in exon 4 of 10, leading to a truncated or non-functional *FIBP* protein compatible with TROFAS. The loss of *FIBP* function impairs its interaction with growth factors, contributing to dysregulated growth and tumorigenesis, fitting with the observed overgrowth and tumor predisposition in TROFAS. Unlike previously reported cases, our patient did not present with macrosomia, tall stature, macrocephaly, or renal anomalies. However, she shared several overlapping features, including facial dysmorphism, intellectual disability, skeletal abnormalities, and cardiac defects. Additionally, varicose venous enlargement, previously reported in the 23-year-old male described by Thauvin-Robinet et al. (12), was also present in our patient, this feature has not been consistently observed in other cases. Further imaging revealed that our patient also had multiple hemangiomas scattered throughout the body.

Segmental overgrowth syndromes are associated with segmental mosaicism, where a postzygotic variant arising during embryogenesis disrupts tissue growth regulation. Overgrowth can result from either increased cell size (hypertrophy) or increased cell proliferation (hyperplasia), with the severity of symptoms depending on the affected gene and its role in cellular growth and survival (14).

Syndromes associated with somatic *PIK3CA* variants are classified under the PIK3CA-Related Overgrowth Spectrum (PROS), which encompasses conditions such as fibro adipose overgrowth (FAO), hemihyperplasia-multiple lipomatosis (HHML), dysplastic megalencephaly (DMEG), congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal anomalies (CLOVES syndrome), Klippel-Trenaunay syndrome, macrodactyly, and others. These disorders share a common genetic origin but present a broad range of phenotypic expressions, from isolated macrodactyly to more complex cases. The variability in symptom severity is influenced by the timing and cellular context of the variant during development (15, 16).

Other genes in the PI3K signaling pathway, including *PTEN* (a negative regulator), are also implicated in segmental overgrowth syndromes. Loss-of-function variants in *PTEN* increase PIP3 levels, activate the AKT/mTOR pathway, and lead to conditions such as germline and mosaic forms of *PTEN* Hamartoma Tumor Syndrome (PHTS). For instance, SOLAMEN syndrome results from a mosaic loss of *PTEN* function and is characterized by localized hypertrophy, vascular malformations, macrodactyly, and an increased cancer risk. Additionally, activating variants in genes such as *PIK3R2*, *AKT1*, *AKT2*, *AKT3*, and *CCND2* have been identified. Somatic activation of *AKT1* is associated with Proteus syndrome, which is marked by asymmetrical lesions, lipomatous tumors, lymphovascular malformations, and overgrowth of bones and connective tissues, also with a higher cancer risk (17, 18).

The presence of a prominent hemangiomatous lesion, along with intellectual disability, excessive soft tissue and bone overgrowth, skeletal abnormalities, and an increased risk of tumors, led us to evaluate the possibility of segmental overgrowth syndromes. TROFAS affects similar genetic pathways and presents comparable clinical features, it can be included within the PROS (*PIK3CA*-Related Overgrowth Spectrum). Our patient was thoroughly evaluated for other overgrowth syndromes (16, 19). Since *PIK3CA* mosaicism may be present in the affected tissues, it was impossible to completely rule out other diseases in this group for our patient.

Recent research suggests that *FIBP* regulates the expression of the mTOR/STAT3 pathway, a signaling molecule implicated in carcinogenesis, which provides a potential mechanism for the increased cancer risk observed in overgrowth syndromes (20). *FIBP* overexpression has been reported in tumors such as colon carcinoma and head and neck cancers. Considering that FGF1 is linked to several cancers, it is hypothesized that the interaction between *FIBP* and FGF1 plays a role in tumorigenesis (5, 21-23).

Our case is particularly notable due to the early onset of multiple malignancies. By the age of 16, the patient had developed two distinct cancers: thyroid follicular carcinoma and mucoepidermoid carcinoma of the parotid gland. Among the eight reported cases of TROFAS in the literature, only a single instance of Wilms' tumor has been documented (13). This case highlights the diversity of malignancies and broadens the spectrum of cancer predisposition associated with *FIBP* gene variants.

Conclusion

Our case is significant for its distinct phenotypic features and the early development of malignancies, underscoring the role of *FIBP* variants in overgrowth syndrome and cancer predisposition. It is also noteworthy that individuals with segmental overgrowth are not always macrosomic at birth, and their height and weight during childhood may remain within normal ranges, highlighting the variability in clinical presentation.

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Figure 1. A. The patient's hand is noticeably larger than a normal hand. **B.** Capillary malformation (Porto-wine Stain) on the hand extending to the arm and contracture of the fingers due to vascular anomalies

1A



1B



Figure 2.

A. Varicose veins.

B. Port-wine-Stain on legs and feet, wide ankles, and feet.

C. Syndactyly between the second and third toes of the left foot.

2A



2B



2C



	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Present Case
Age	17 years, male	14 years, female	10 years, male	3 years, female	4 years, male	16 years, male	5 years, female		16 years, female
Macrosomia	+	+	+	-	+	-	-	+	-
Tall Stature	+	+	+	+	+	+	+		-
Intellectual Disability/Developmental Delay	+	+	+	+	+	+	+	+	+
Macrocephaly	+	-	-	-	+	+	+		-
Cardiovascular Anomalies	VSD MVP Varicose veins	VSD Double chamber right ventricle	-	-	Small PDA Multiple telangiectasias	Minimal pericardial effusion	-	-	Varicose veins Hemangiomas Hepatic artery originating from the abdominal aorta Mild MVP Small ASD
Genitourinary Anomalies	Renal malrotation Left bifid ureter	-	-	Cystic dysplastic kidneys	Mild right renal pelvis dilatation Unilateral cryptorchidism	Right renal atrophy	-	-	-
Hearing loss	-	+	-	-	-	-	-	-	-
Dysmorphic Features	Occipital prominent aspect Long and down-slanting palpebral fissures Large and prominent ears Thick lips Mild macroglossia	Round face Widely spaced eyes Epicanthic folds Depressed nasal bridge Short, small nose Flat mid-face and full lips	Round face Widely spaced eyes Epicanthic folds Depressed nasal bridge Short, small nose Flat mid-face and full lips Strabismus	Round face Widely spaced eyes Epicanthic folds Depressed nasal bridge Short, small nose Flat mid-face and full lips	Triangular face Mid-face retrusion Pointed chin Deeply set eyes Hypertelorism Long and wave-shaped palpebral fissures Prominent nasal bridge Short philtrum High palate, Posteriorly rotated ears and uplified earlobes Thick and broad eyebrows with mild synophrys Hypoplastic nipples	Macrocephaly Round face Widely-spaced deep-set eyes Prominent supraorbital ridges Thick eyebrows Down-slanting palpebral fissures Marked philtrum	Round face Flat Midface Widely-spaced eyes Thick eyebrows Marked philtrum.	Hypertelorism Thick and arched eyebrows Pointed chin Down-slanting palpebral fissures Epicanthic folds Broad nasal bridge Small nose High palate	Flat midface Mild right ptosis Low palpebral fissures Deep-set eyes Thick lips Thick and broad eyebrows Mild synophrys Pointed chin Prominent nasal bridge Narrow forehead High palate Posteriorly rotated ears and raised earlobes
Skeletal Abnormalities	Hands and feet were large with large thumbs and hallux Bilateral asymmetric limitation of thumb extension Spatulate digits Camptodactyly		Bilateral talipes equino varus, Rotation of both femurs and tibiae Spina bifida occulta		Narrow chest Mild pectus excavatum, Hyperextensible elbow joints Pes planus	Scoliosis Pectus deformity Thoracic asymmetry Large hand Large feet Talipes varus	-	Coxa valga	Mild pectus excavatum and pes planus Enlarged hands and feet
Other	Bilateral retinal coloboma Transient neutropenia. Inguinal hernia Psychosis	Chronic benign neutropenia	Chronic benign neutropenia	Polyhydramnios	Multiple nevus Fibrotic changes in bilateral basal lung segments consistent with chronic pulmonary disease	Parieto-occipital perivascular cystic gliotic changes Slightly decreased muscle strength in the lower extremities	Cerebral periventricular patchy hyperintense lesions	-	Port-wine stains on the arms and legs Widespread nevi on face and trunk

Tumor/Cancer Predisposition	-	Wilms Tumor	-	-	-	-	-	-	Parotis low-grade mucoepidermoid carcinoma Thyroid follicular carcinoma
<i>FIBP</i> gene variant	Homozygous NM_004214.5 c.652C>T	Homozygous NM_198897.1 c.175_176insTAA	Homozygous NM_198897.1 c.175_176insTAA	Homozygous NM_198897.1 c.175_176insTAA	Homozygous NM_004214.5 c.415_416insCAGTTTG	Homozygous NM_004214.5 c.412-3_415dupCAGTTTG	Homozygous NM_004214.5 c.412-3_415dupCAGTTTG	Homozygous NM_004214 c.412-3_415dupCAGTTTG	Homozygous NM_004214.5 c.412-3_415dup
Author	Thauvin-Robinet et al. 2016	Akawi et al. 2016	Akawi et al. 2016	Akawi et al. 2016	Düzenli et al. 2023	Kılıç et al. 2023	Kılıç et al. 2023	Yüksel Ülker et al. 2024	

Table 1. Clinical and Genetic Characteristics of the Nine Reported Cases of Thauvin-Robinet-Faivre Syndrome (TROFAS)

ASD: Atrial Septal Defect, VSD: Ventricular Septal Defect, MVP: Mitral Valve Prolapse, PDA: Patent Ductus Arteriosus