pathogenic variant in the *POGZ* gene causative of the White-Sutton syndrome (MIM#616364). The *POGZ* gene is located on chromosome 1q21.[6] *POGZ* is a pogo transposable element–derived protein with a zinc finger domain that binds to HP1alpha, destabilizing the HP1alpha-chromatin interaction, and thus acts as a chromatin regulator.[7] This gene is constitutively expressed throughout the body but reaches its highest expression during the embryonal period of development, around weeks 8-9.[6] *POGZ* expression has been documented in lens fiber cells during human embryogenesis.[8]

Currently, there are approximately 100 reported cases of the syndrome.[9] Common features of White-Sutton syndrome include developmental delay and intellectual disability, autism spectrum features, brain anomalies, facial dysmorphisms, feeding difficulties, renal abnormalities, and audiological and visual disturbances.[9] Common ophthalmic anomalies associated with the syndrome include strabismus, hyperopia, astigmatism, and rod-cone retinal dystrophy.[10] Our patient presented with microcephaly, feeding difficulties, and hydronephrosis, which are consistent with White-Sutton syndrome. Neuropsychiatric assessments for autism are pending, given the patient's young age.

In summary, in the evaluation of infants with bilateral corneal opacity and systemic abnormalities, trio analysis with whole exome or genome sequencing may reveal additional diagnoses not initially considered. Given that the White-Sutton syndrome has only been described recently and because of the considerable variety of associated ophthalmologic disturbances, it might be an important diagnosis to consider when evaluating a patient with congenital corneal opacities.

Literature Search

The following databases were searched from March 1 to March 15 ,2022: PubMed/NLM, LISTA/EBSCO, EMBASE, Web of Science, ProQuest, and Ovid. Search terms consisted of combinations of the following: *White-Sutton*, *POGZ*, *congenital*, *cornea*, and *opacities*. No exclusions were made based on timeframe of publication, and the search was not restricted by language of publication. Articles that discussed White-Sutton syndrome were evaluated for reports of ophthalmologic manifestations, then congenital corneal opacities.

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New ocular findings in a patient with a novel pathogenic variant in the *FBXO11* gene

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Intellectual developmental disorder with dysmorphic facies and behavioral abnormalities (IDDFBA) is a recently described autosomal dominant entity caused by pathogenic variants, mostly de novo, in the *FBXO11* gene. It presents in the first years of life with highly variable clinical manifestations. The main features of IDDFBA include borderline-to-severe intellectual disability, behavioral problems, hypotonia, facial dysmorphisms, minor skeletal abnormalities, and recurrent infections. Although eye problems, such as refractive errors, eye misalignment and minor visual changes, have been described in about 48% of patients, a major ocular defect, namely, bilateral optic nerve hypoplasia, has been reported in the literature only once. We report an 8-year-old boy with a novel de novo pathogenic variant in *FBXO11* gene (NM_001190274.1: c.1166dup, p.Cys390Metfs*3) and a complex ophthalmological phenotype, consisting of right microphthalmia, very shallow anterior chamber, and persistent pupillary membrane, right dense

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Submitted February 23, 2022.
Revision accepted May 15, 2022.
Published online August 5, 2022.

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J AAPOS 2022;26:268-270.

1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2022.05.008

nuclear cataract, bilateral optic nerve hypoplasia, and bilateral horizontal manifest nystagmus.

Case Report

We describe an 8-year-old boy, who was born to healthy, nonconsanguineous parents at 39 weeks' gestation by vaginal birth after an uneventful pregnancy. Birth weight was 2,980 g (10th centile), length was 50 cm (50th centile), and head circumference (HC) was 34 cm (5th centile). Apgar score was 9/10. Postnatal microcephaly (HC < 3rd centile), mild acral anomalies, hypotonia, and mild developmental delay were recognized at the age of 4 months. He sat unsupported after 8 months, crawled after 12 months, and said his first single words at 18 months of age. From 3 years of age, moderate psychomotor delay and aggressive behavior were noted. Developmental assessment at 4 years and 6 months documented attention deficit hyperactivity disorder, poor expressive language, and major difficulties with social interaction, fine motor skills, and motor coordination. At 7 years of age, he presented moderate intellectual disability.

Ophthalmological examination, at 4 months of age, documented the following in the right eye: microphthalmia, very shallow anterior chamber, persistent pupillary membrane, and dense nuclear cataract that made visualization of the fundus impossible. The anterior structures in the left eye were normal. Fundus examination of the left eye was suggestive of mild optic nerve hypoplasia. Magnetic resonance imaging of the brain at 4 months of age confirmed right microphthalmia with a very shallow anterior chamber and revealed hypoplasia of the prechiasmatic segment of the right optic nerve, with features suggestive of extensive retinal detachment. At about 9 months of age, he underwent right eye evisceration and placement of a prosthetic eye. On his last examination at age 7, best-corrected visual acuity in the left eye was 20/40. Bilateral horizontal manifest nystagmus was damped by an abnormal head posture (left rotation and right tilt). Fundus photography and optical coherence tomography confirmed mild-to-moderate left optic nerve hypoplasia (Figure 1).

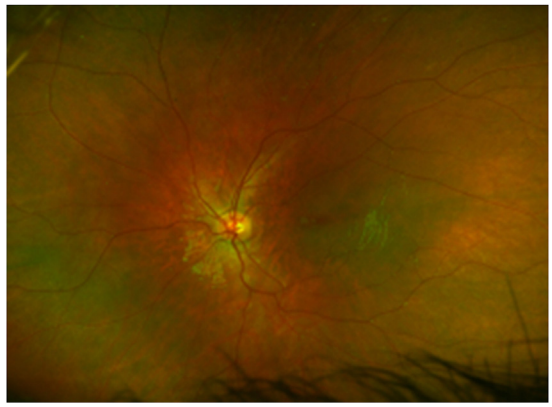

FIG 1. Left eye fundus image (optomap; Optos Inc, Marlborough, MA), obtained at 6 years of age, displaying mild-to-moderate optic nerve hypoplasia (optic nerve diameter, 1.4 mm; total disk area, 1.56 mm^2).

On physical examination, he presented with minor dysmorphisms (Figure 2), namely, facial asymmetry, thin eyebrows, upslanting palpebral fissures, bulbous nasal tip, prominent left ear, thin upper lip, and retrognathia. Mild acral anomalies were also noted, including puffy and tapered fingers, clinodactyly of the fifth finger, slightly broad hallux, sandal gap, clinodactyly of the second toe, and deep sole creases.

Cytomegalovirus infection was excluded, and extensive neurometabolic investigation was negative. Array comparative genomic hybridization (CGX-HD 180K, Signature Genomics, PerkinElmer, Lisbon, Portugal) excluded the presence of clinically relevant copy number variants. Based on the clinical picture, pathogenic variants in *KIF11*, *CREBPP*, and *EP300* genes were initially ruled out.

Trio whole exome sequencing (WES) was performed when the patient was 7 years of age but did not identify any variant that could explain the observed phenotype. In 2021, WES data reanalysis uncovered the presence of a novel heterozygous de novo frameshift pathogenic variant

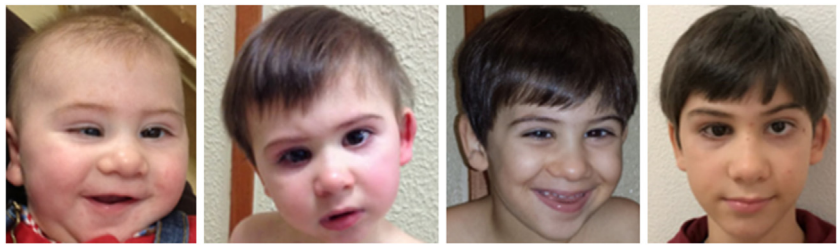

FIG 2. Patient at 1 year of age, 1 year and 5 months, 3 years, and 6 years (left to right). Note minor facial dysmorphism with facial asymmetry, thin eyebrows, upslanting palpebral fissures, bulbous nasal tip, prominent left ear, and thin upper lip.

in the *FBXO11* gene, for which loss-of-function is a known disease mechanism, located in a highly conserved position and not found in gnomAD exomes or genomes (NM_001190274.1): c.1166dup, p.(Cys390Metfs*3) (ACMG classification: 5/PVS1-VS, PM2-S, PS2-S criteria).

Discussion

FBXO11 is part of the SCF (SKP1-cullin-F-box) complex, a multiprotein E3 ubiquitin-ligase complex that catalyzes the ubiquitination of proteins destined for proteasomal degradation.[1,2]

In 2018, heterozygous pathogenic variants in the *FBXO11* gene were linked to intellectual developmental disorder with dysmorphic facies and behavioral abnormalities (IDDFBA, *OMIM#618089*).[2] To our knowledge, 71 cases have been reported in the literature so far.[1-5]

The mutational spectrum encompasses large multigene and intragenic deletions, expected to be gene-disrupting variants, as well as single amino acid deletions, frameshift, nonsense, and missense variants, distributed across the entire gene.[3,4] No mutational hotspots or mutation types predominate, in keeping with the intolerance of *FBXO11* to loss-of-function variants; this helps to explain why no obvious genotype-phenotype correlations have been established yet.[3,4]

All patients presented with ID (71/71),[3] albeit of variable severity, and shared some overlapping dysmorphisms, namely, high broad forehead, long palpebral fissures, and thin upper lip with a broad space between its paramedian peaks (65/68).[3,4] A variety of behavioral abnormalities were also common (48/68), such as poor social interaction, autistic features, stereotypic movements, hyperactivity, short attention span, and aggressive outbursts.[1,3,4] Although there is no typical gestalt,[1,3,4] our patient's features and neurobehavioral phenotype are consistent with the literature. Other characteristics, namely, microcephaly (15/68) and hypotonia (44/63), are present in many individuals with IDDFBA. A range of eye manifestations, such as strabismus, hypermetropia, progressive high myopia, pseudoesotropia, and lacrimal duct obstruction, have been reported in the literature (32/66).[1,3,4] Only one individual presented with a more pronounced visual deficit due to bilateral optic nerve hypoplasia.[4]

Microphthalmia is a congenital anomaly affecting the posterior and/or the anterior segment of the eye (mean eye axis length, <18.5 mm). If associated with other ocular malformations, which is usually the case, it is termed *complex* microphthalmia.[6] The condition has a heterogeneous etiology, including chromosomal rearrangements, deleterious variants in several genes causing nonsyndromic (with *SOX2* as a major causative gene in this group), or syndromic microphthalmia (Norrie disease, CHARGE syndrome, Walker-Warburg syndrome, among others), and environmental causes (congenital cytomegalovirus or rubella infections, maternal alcohol intake, maternal phenylketonuria).[6] In the present case, array comparative genomic hybridization and trio WES did not detect clinically relevant CNVs or SNVs in genes associated with microphthalmia, and known environmental etiologies were also excluded.

Our patient presented with bilateral optic nerve hypoplasia and right microphthalmia with severe atrophy of the prechiasmatic segment of the optic nerve. To our knowledge, this is the first report of such a severe ocular phenotype in IDDFBA[4], adding *FBXO11* to the list of genes causative for complex microphthalmia. These findings also stress the fact that this new entity should be considered in the differential diagnosis of cytomegalovirus infection.

Our patient's complex ocular phenotype expands the clinical spectrum associated with pathogenic variants in the *FBXO11* gene. Moreover, this case illustrates the advantages of WES reanalysis in achieving a molecular diagnosis in syndromic ID patients where initial sequencing was unrevealing. In the clinical setting it is essential to collect and share data about such rare genetic entities in order to help define their clinical spectrum and inform both medical follow-up and genetic counseling.

Literature Search

PubMed was searched, without language or date range restriction, on December 30, 2021, using the following terms: FBXO11, *microphthalmia*, and *intellectual developmental disorder with dysmorphic facies and behavioral abnormalities (IDDFBA)*. Google Scholar was searched on January 2, 2022, using the term FBXO11 *developmental disorder*. Science Direct was searched on January 10, 2022, using the terms FBXO11 and *bilateral optic nerve hypoplasia*.

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