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Ophthalmologic findings in an 18-month-old boy with focal dermal hypoplasia

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Abstract

Focal dermal hypoplasia is a rare X-linked dominant disorder with in utero lethality in males. Affected patients have been reported to have several different mutations in the *PORCN* gene on chromosome Xp11.23. Dysplastic mesodermal and ectodermal tissue causes clinical findings in the skin, skeleton, teeth, central nervous system, and eyes of affected patients. We describe the ophthalmologic findings in an 18-month-old boy with mosaicism of a novel mutation in *PORCN*.

Case Report

An 18-month-old boy presented to Moran Eye Center, Salt Lake City, for evaluation of bilateral iris colobomas and left esotropia. He was previously seen by the Division of Medical Genetics and diagnosed with Goltz-Gorlin syndrome (GGS), or focal dermal hypoplasia (FDH, MIM 305600), with clinical findings of syndactyly, split foot malformation, possible osteopathia striatum, nail dystrophy, cutis aplasia, dermal hypoplasia, and simplified ears with underdevelopment of the superior helices and ocular colobomas. He was also examined by a cardiologist for pulmonary hypertension and atrial septal defect.

DNA extracted from a peripheral blood sample was amplified with polymerase chain reaction (PCR) for genetic analysis. Exons 1-14 and flanking splice sites of the *PORCN* gene were amplified and sequenced bidirectionally with the published gene sequence until the mutation was found. Duplication of a single A nucleotide in exon 10 (c.956dupA) of the *PORCN* (PORCUPINE, DROSOPHILA, HOMOLOG OF) gene was identified in some, but not all, cells. This mutation causes a frameshift and creates a premature stop codon at position 99 of the new reading frame and is predicted to cause loss of normal protein function through protein truncation or nonsense-mediated mRNA decay.

On ophthalmological examination, the patient was able to fix and follow with each eye, although he would not maintain fixation with the left eye. Binocular Teller visual acuity was

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4.8 cy/cm. Pupils were minimally reactive secondary to sizeable inferonasal iris colobomas. Assessment of his ocular alignment revealed a left esotropia of 40^{Δ} and a small amplitude, moderate frequency manifest nystagmus. Large, bilateral chorioretinal colobomas were seen on dilated fundus examination.

Examination under anesthesia was performed. Intraocular pressures were normal. Cycloplegic refraction revealed moderate, myopic astigmatism in each eye (right eye, −6.50 +1.50 × 170; left eye, −5.00 +1.00 × 170). The corneas were clear and measured 10 mm in diameter in the right eye and 9 mm in the left eye. Bilateral inferonasal iris colobomas were present; no lens coloboma was noted. Dilated fundus examination of the right eye showed a large, inferior coloboma that bisected the macula and encompassed a malformed optic disk that gave the appearance of two optic nerve heads (Figure 1). The yellow appearance within the presumed fovea suggested the presence of xanthophyll. There was a retinal flap tear near the ora serrata of the right eye. In the left eye, a larger, inferonasal chorioretinal coloboma involved the entire macula. Neither a central retinal artery nor a definite optic disk could be discerned, but 3 regions of incompletely developed optic disks were present (Figure 2). Small, hypopigmented, patches were present supranasally, and areas (Figure 2) suggesting defects of the retinal pigment epithelium were seen temporally. A definitive ora serrata was absent from 7 to 2 o'clock. Electroretinography was normal in the right eye and slighty subnormal in the left eye. Flicker testing (30 Hz) was in the low-normal range in each eye. Visual evoked potentials were subnormal in both eyes and worse in the left eye.

Fundus photography and fluorescein angiography were performed (RetCam; Clarity Medical Systems, Pleasanton, CA). In the left eye a substantial delay in vascular filling was noted; the choroidal vasculature began to fill at 26 seconds but only completely filled by 43 seconds. Three retinal vascular systems appeared to fill from choroidal vessels—an inferonasal vessel filling first at about 39 seconds (Figure 3A) and the other vascular systems by 43 seconds (Figure 3B). Complete filling of the retinal circulation did not occur until after 93 seconds. The right eye also appeared to have two separate vascular complexes associated with an abnormal divided optic disk.

Peripheral laser retinopexy was performed in the right eye around the flap tear.

Discussion

Focal dermal hypoplasia is a rare genetic disorder characterized by a constellation of findings involving skin (atrophy and linear pigmentation and herniation of fat through the dermal defects occurring along the lines of Blaschko), skeletal (limb hypoplasia, syndactyly, polydactyly, oligodactyly), dental (hypoplastic teeth), central nervous system (developmental delay), and ophthalmologic (anophthalmia, coloboma, corneal clouding, strabismus) anomalies.[1]

Mutations in the *PORCN* have been described not only in FDH but also in cases of pentalogy of Cantrell and limb-body wall complex.[2] PORC proteins are thought to be involved in palmitoylation of Wnt signaling proteins, which play key roles in embryonic tissue development, particularly that of the dermis and skeleton.[3] Wnt signaling involving

the ligand Norrin is important in retinal vascular development. Abnormalities in Norrin can lead to Norrie disease or X-linked familial exudative vitreoretinopathy.[4]

FDH is lethal in males, but males are affected in about 10%-15% of FDH cases as a result of somatic mosaicism for a post-zygotic mutation or X-chromosomal aberrations.[5]

Ophthalmologic pathology occurs in 40% of patients with FDH and can include aniridia, strabismus, lens subluxation, microphthalmos, retinal pigment changes, optic atrophy, vitreous debris, ectropion, ptosis and nasolacrimal duct obstruction.[6] There are reports of colobomatous retinal detachment and peripheral retinal nonperfusion with subsequent neovascularization and hemorrhage requiring retinal photocoagulation.[7,8]

We report a novel, somatic mutation in *PORCN* leading to mosaicism in a young male patient and detail the clinical phenotype, which suggests dramatic abnormalities in the development of the optic nerves and retinal vasculature. Such descriptions will not only provide insight into genotype-phenotype correlations in FDH but will also advance our understanding of Wnt signaling and its role in embryogenesis.

Literature Search

PubMed was searched, most recently on August 22, 2013, for literature in English using the following search terms: *Goltz syndrome*, *focal dermal hypoplasia*, *Wnt*, and *PORCN*.

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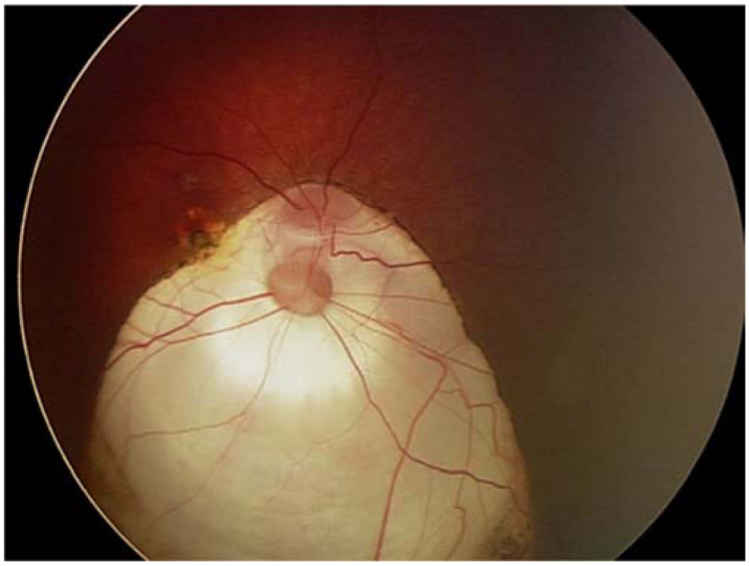

FIG 1.

Inferonasal chorioretinal coloboma (right eye) that bisects the macula and encompasses a malformed optic nerve head appearing as two optic disks; yellow pigmentary changes give the appearance of xanthophyll.

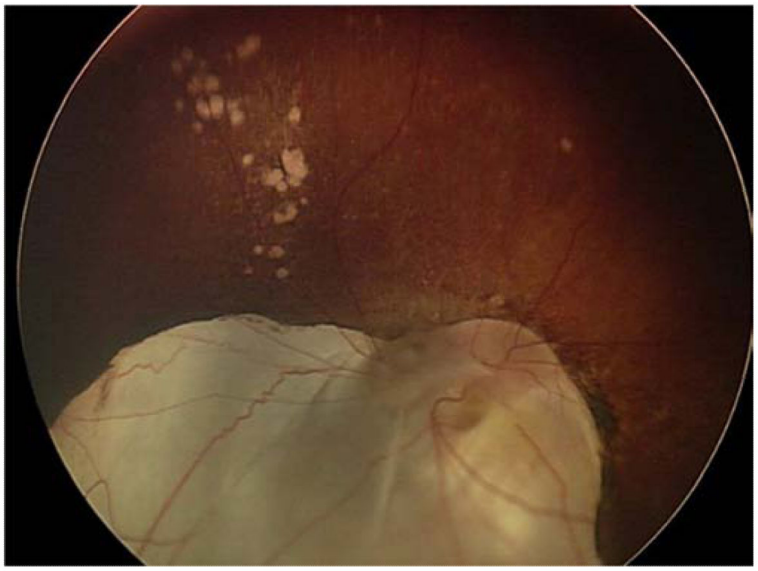

FIG 2.

Chorioretinal coloboma (left eye) with an abnormal optic disk suggesting 3 regions of underdeveloped optic nerve tissue without a discernible central retinal artery; note small hypopigmented lesions superonasally that simulate small colobomas or areas of atrophy.

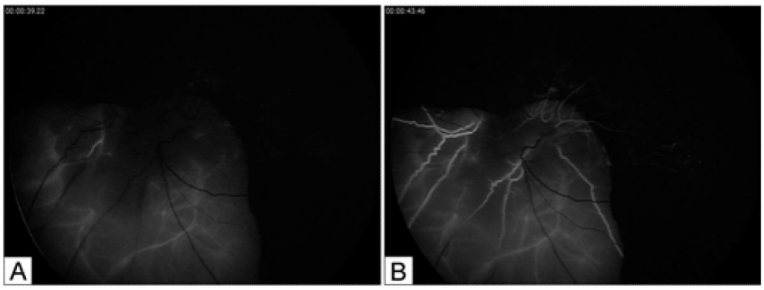

FIG 3.

A, Fluorescein angiography showing an inferonasal retinal vessel filling from the choroid at about 39 seconds. B, The choroid is completely filled at 43 seconds and supplies overlying retinal vessels; window defects are seen in the absence of overlying pigmented retina.