# Article • A Novel PAX6 Mutation in a Patient with Nonsyndromic Dominant Foveal Hypoplasia and Congenital Nystagmus

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## ABSTRACT

**Background:** Foveal hypoplasia is a disorder in which the fovea does not develop normally. It is commonly associated with congenital nystagmus and other developmental conditions, such as aniridia and albinism.

**Case Report:** We examined a 15-year-old female who presented with foveal hypoplasia and congenital nystagmus in the absence of any systemic or anterior segment abnormalities. Genetic testing showed a novel PAX6 missense mutation.

**Conclusion:** This report highlights a case of autosomal dominant, isolated foveal hypoplasia with a novel PAX6 mutation without any anterior segment anomalies.

**Keywords:** autosomal dominant, foveal hypoplasia, nystagmus, ocular anomalies, PAX6 gene

## Introduction

Foveal hypoplasia results from improper development of the retina. It is characterized by a lack or reduction of the foveal pit, with the presence of all inner retinal layers within the foveal region.[1] Nystagmus is a common ocular finding in patients with foveal hypoplasia. Other findings or conditions may include: aniridia, albinism, corneal anomalies, premature cataracts, keratitis, optic nerve anomalies, or iris hypoplasia.[2-4] Cataract onset can occur in a patient's second or third decade of life but has been documented as early as age 13.[5]

Here, we present a case in which a teenager had a novel autosomal dominant PAX6 missense mutation associated with foveal hypoplasia and nystagmus without the presence of anterior segment anomalies, cataract formation, or associated systemic findings. Nonsyndromic autosomal dominantly inherited foveal hypoplasia associated with a PAX6 mutation is rare.

## Case Report

A 15-year-old Caucasian female presented with complaints of difficulty seeing at a distance with her current glasses. Her medical history was unremarkable. There was a strong paternal family history of nystagmus, including her father, paternal aunt, paternal grandfather, and paternal great grandfather (Figure 1). The patient was last seen in our office at 3 months of age and was diagnosed with foveal hypoplasia. The patient's father was examined by the authors at the patient's initial visit. An examination of his anterior segment was unremarkable for any anomalies, while an examination of his fundus showed foveal hypoplasia and a prominent nystagmus. An optical coherence tomography (OCT) measurement confirmed the diagnosis of foveal hypoplasia for the patient's father. The patient's father and other relatives were not available for genetic testing or further examination.

The patient's best-corrected visual acuity was 20/50, with a moderate myopic and astig-

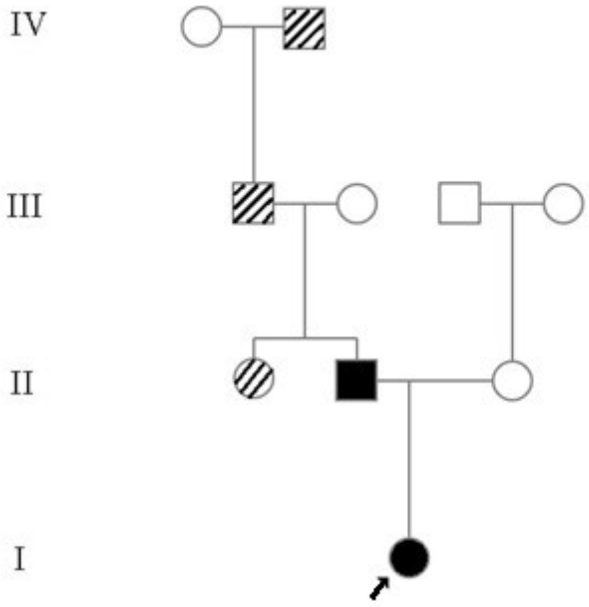


***Figure 1.*** *Pedigree of patient's family documenting autosomal dominant transmission. The cross-hatching pattern indicates that the individual is affected per history. The solid black pattern indicates that the individual is affected. The squares represent males, and the circles represent females. The proband is noted by an arrow.*

matic correction in each eye. Color vision testing using Ishihara plates was normal in each eye, as were the intraocular pressures of 14 mmHg. Anterior segment findings included mild bilateral ptosis, encroachment of limbal vessels (characteristic of a contact lens wearer), and a mildly fibrillar vitreous in each eye on slit lamp biomicroscopy. No evidence of cataracts, corneal anomalies, or iris anomalies was detected in either eye. The patient had a low-amplitude, high-frequency, pendular nystagmus in each eye. Posterior segment findings were within normal limits, with the exception of the macula. There was no evidence of a foveal reflex or any macular pigmentation in either eye. Spectralis HRA+OCT (Heidelberg Engineering Inc., Massachusetts, USA) imaging showed an absence of the foveal pit and continuation of all retinal layers within the

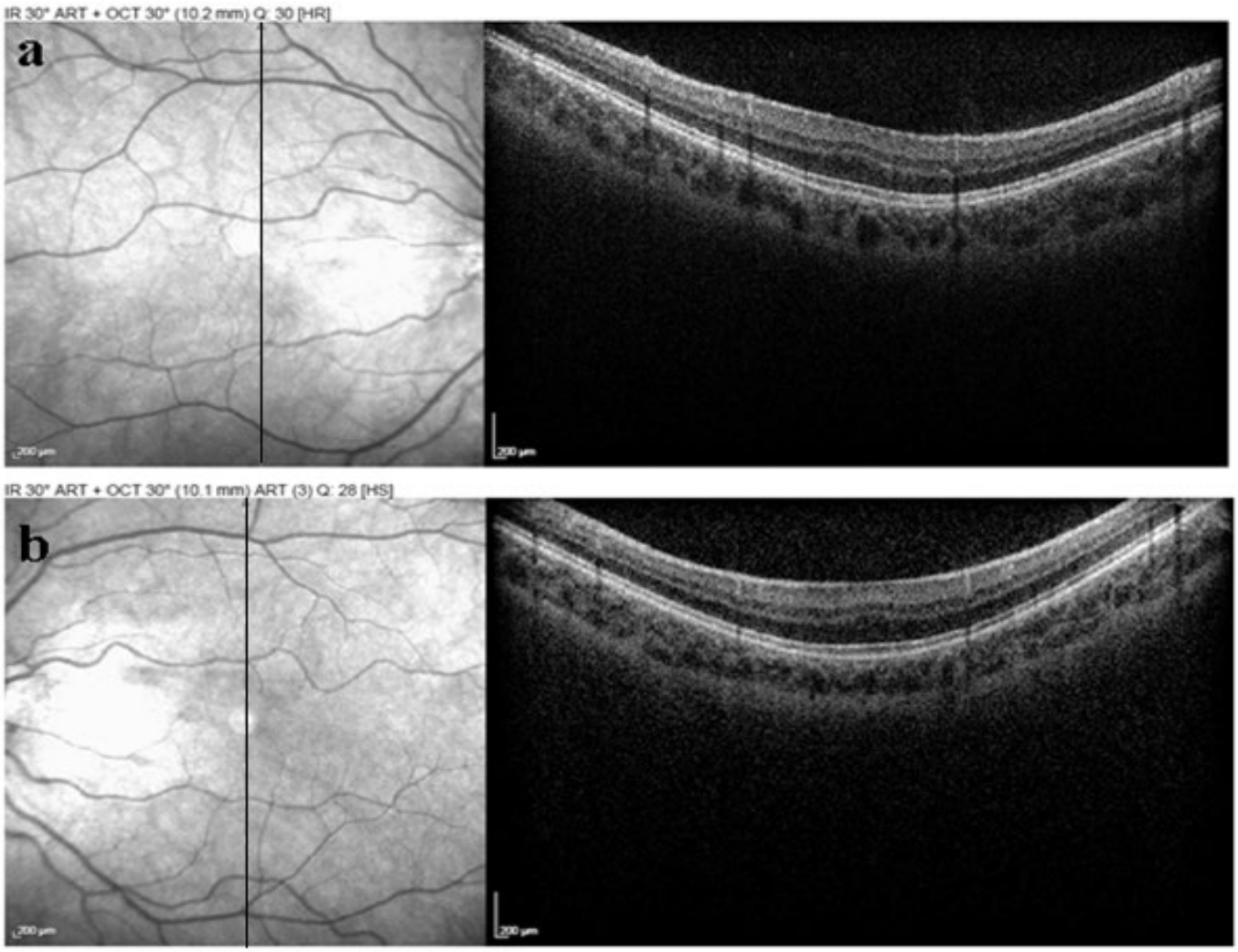


***Figure 2.*** *No foveal pit is evident on OCT imaging in either the patient's right eye (a) or left eye (b). All inner retinal layers extend through the foveal region in each eye. The vertical line on the leftmost image represents the orientation of the cross section represented in the rightmost image.*

fovea (Figure 2). Goldmann visual field testing was normal, both centrally and peripherally, to a III4e and II4e target in each eye.

After parental consent and patient assent, forms were signed. We performed a single gene (PAX6) Sanger sequence analysis to determine the patient's genetic mutation. Since only a single gene was being screened, there was no risk of incidentally discovering a life-threatening or occult disease. A novel heterozygous missense variant was identified in the PAX6 gene, namely p.Arg142His:c.425G>A. The p.R142His:c.425G>A variant is not in the gnomAD database or in the ClinVar database. The variant was predicted to be damaging by PolyPhen-2, SIFT, and Mutation Taster, and it was designated as likely pathogenic by VarSome. The patient and her family were counseled on the 50% probability for future offspring developing a similar affliction. As the patient's mutation was identified, the option of very early diagnosis in her future offspring was discussed. Also, having identified a PAX6 mutation, we could counsel the patient that she has a nonprogressive ocular disease. We discussed how a referral to our low vision clinic would be helpful for evaluating the possible benefit of a bioptic lens or telescope to aid in distance vision: for example, when at a concert, movie theatre, sporting event, and possibly for driving with an unrestricted license.

## Discussion

PAX6 (11p13) is a gene that is expressed in developing ocular structures and the central nervous system. The PAX6 mutation is believed to encode a transcription factor,[6,7] and thus mutations in this gene can lead to underdevelopment of these two structures. Congenital cataracts, aniridia, and anterior segment anomalies are thought to be caused by a mutation in the PAX6 gene with an impaired regulation of crystallin function.[6] There are theories as to why foveal hypoplasia is associated with PAX6 mutations. The human fovea develops at around 30 weeks of gestation; at this time, mitotic cells have been shown to express PAX6.[6] It is thought that a malfunction of the PAX6 gene at this later stage of development can cause poor differentiation within the foveal area, resulting in foveal hypoplasia.[6] There have been only a few documented cases of nonsyndromic foveal hypoplasia with a known PAX6 mutation.[8] This manuscript highlights this uncommon presentation and underpins the value for the screening of PAX6 mutations in patients with isolated foveal hypoplasia even in the absence of iris defects.[5] A careful slit lamp biomicroscopic examination of the iris is mandatory since defects in the iris can be subtle.


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Human Subjects and Informed Consent: All research was in accordance with the tenets of the Declaration of Helsinki. Informed consent or assent was obtained from all subjects after a thorough explanation of potential risks/benefits and the purpose of the study was provided. This research endeavor was approved by the Western Institutional Review Board (IRB).

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