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Case Report
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Novel Mutations in the *PAX6* Gene in Type I in Central Foveal Hypoplasia (FVH1): Case Report

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Abstract

Purpose: Foveal Hypoplasia (FH) is a rare retinal disease; we report a case of the medical records and genetic confirmation of the *PAX6* gene in a child with FVH1.

Case Report: A 6-year-old Chinese boy presented to our hospital for visual developmental impairment. Born at term without systemic abnormalities. Both eyes had positive ocular position, with a decimal Best Corrected Visual Acuity (BCVA) of 20/50, right eye of 20/60, diopter of -1.00DC and left eye, 20/50, and diopter of -1.50DC. The child did not have a nystagmus. Slit lamp examination revealed normal cornea, anterior chamber, iris, and lens. The retinal vessels on bilateral fundus examination were symmetrical and without distortion. However, the retinal fovea was not reflective. SD-OCT showed that there was no obvious central retinal pit in the right eye, the shallow central retinal pit in the left eye, and the persistence of the inner retina. The ERG results showed a decrease in both binocular and darkroom visual functions. The parents had no ocular abnormalities.

Discussion: The case had signs and symptoms of visual development disorder. The SD-OCT images showed the lack of a prominent macular central pit. Examination of the *PAX6* gene revealed that the child had a novel heterozygous mutation c.127_135del (p.Ser43_Ile45del).

Conclusion: A heterozygous mutation in the *PAX6* gene can cause FVH1. FVH1 is difficult to diagnose, but a detailed observation of its macular foveal structure and the whole-exon detection of its genes can help to identify patients with FVH1.

Keywords: Isolated macular foveal dysplasia; FVH1; *PAX6*; Case report

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Introduction

Macular Foveal Hypoplasia (Foveal Hypoplasia, FH/FVH) [1] is a rare retinal disorder which is usually associated with other ocular diseases such as aniridia (OMIM # 106210), microphthalmia (OMIM% 25100), albinism (OMIM # 203100) and color blindness (# 216900) [2-4]. The clinical manifestations are vision loss and nystagmus. Signs were the reduction or absence of a foveal socket and a foveal avascular zone (Foveal Avascular Zone, FAZ). Macular foveal dysplasia is related to autosomal dominant and autosomal recessive inheritance, and type I (FVH 1) is caused by a heterozygous mutation in *PAX6* gene (607108) on chromosome 11p13; type II (FVH2) is caused by a mutation in *SLC38A8* gene (615585) on chromosome 16q23 [5-8].

The diagnosis of FVH1 is based on fundus examination, with diminished or absent macular foveal reflex and disturbed vascular morphology in the macular area. High-resolution Spectral Domain Coherence Tomography (SD-OCT) detects the persistence of the inner retinal layer. Japanese scholars believe that the abnormal reduction of FAZ area shown by OCTA can also provide evidence of foveal hypoplasia [9]. Previously reported vision in children with FVH1 ranged from 20/20 to 20/200. Cases lacking a complete foveal structure with 20/50 vision have been reported [9-10]. We report a case of a FVH1 child with an apparently adverse macular foveal structure but still with 20/50 vision, and genetic testing revealed a mutation in the *PAX6* gene. This study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee (No. [2023]-31). Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. The work has been reported in line with the SCARE criteria.

Case Presentation

A 6-year-old Chinese boy presented to our hospital for visual developmental impairment. Born at term without systemic abnormalities. Previous operated at another ophthalmic institution for common exotropia, the surgical procedure is the retraction of the external rectus muscle of both eyes. Both eyes had positive ocular position, with a decimal Best Corrected Visual Acuity (BCVA) of 20/50, right eye of 20/60, diopter of -1.00DC and left eye, 20/50, and diopter of -1.50DC. The child did not have a nystagmus. Slit lamp examination revealed normal cornea, anterior chamber, iris, and lens (Figure 1A). The retinal vessels on bilateral fundus examination were symmetrical and without distortion. However, the retinal fovea was not reflective (Figure 1B). SD-OCT showed that there was no obvious central retinal pit in the right eye, the shallow central retinal pit in the left eye, and the persistence of the inner retina (Figure 1C). The ERG results showed a decrease in both binocular and darkroom visual functions (Figure 1D). The parents had no ocular abnormalities.

Two (2 mL) mL of each whole blood of children and parents (EDTA anticoagulation), collected samples for whole exome sequencing, whole genome DNA from peripheral blood leukocytes, DNA library building and capture, and 150 bp double-end sequencing. After the raw sequencing data were processed by bioinformatic analysis. The detected SNP and Indel variants were annotated using the ANNOVAR software. The notation information includes chromosome start and termination positions. The reference allele, The alternative allele, Gene function, Population frequency of the public database (including one thousand human genomes, ExAC, GnomAD Data base, etc.), Protein function prediction software results (including REVEL, CLINPRED, SIFT, PROVEAN, MutationTaster, CADD, POLYPHEN2, DBSCSNV11, et al.) and other information. Finally, variant pathogenicity assessment and genetic interpretation of candidate gene variants were performed by referring to the classification criteria and guidelines for the American Medical Genetics and Genomics Society (American College of Medical Genetics and Genomics, ACMG).

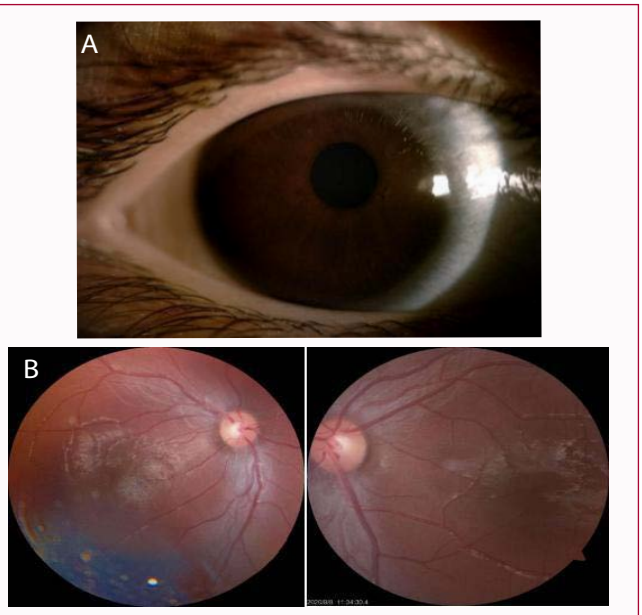

Figure 1: (A) Slit lamp photo-taken. A scleral cornea on the temporal side, and the remaining cornea is still transparent, the anterior chamber depth is acceptable, the iris texture is clear, and the crystal is transparent. (B): Binocular ocular fundus photographs of patients with macular foveal dysplasia. Retinal flat without foveal reflex. The optic papilla boundary is clear, orange-red.

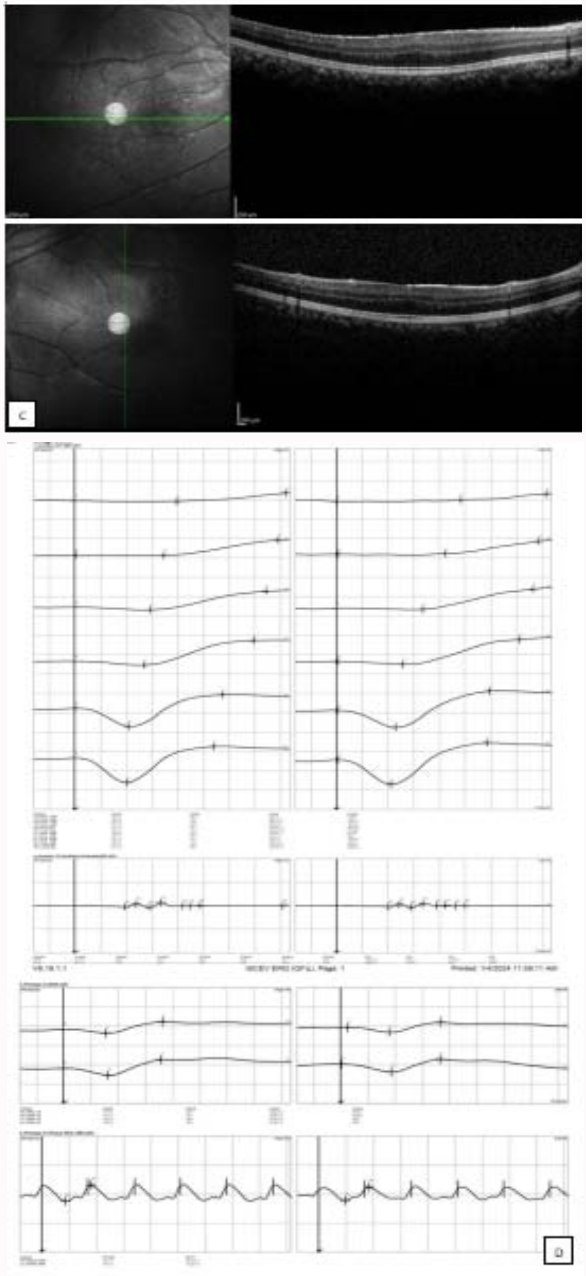

Figure 1: (C): Optical Coherence Tomography (SD-OCT) images of patients with macular foveal dysplasia. There was no apparent central retinal pits in the right eye and the left eye where the inner retinal layers persisted. D) ERG examination results of children: moderate decrease, maximum response a-wave, b-wave light to moderate reduction, peak time delay, OS OS2 moderate decrease, peak time delay, each waves clear, open a-wave moderately lower right eye, left eye, binocular b-wave moderate decrease, peak time delay; and moderate decrease at 30 Hz.

Screening for *PAX6* gene mutations, the child had a novel non-frameshift mutation, c.127_135del (p.Ser43_Ile45del) (NM_000280), which is a heterozygous variant and newly verified by first-generation sequencing (Figure 2).

Discussion

The normal macular fovea lacks the inner retinal layer and is

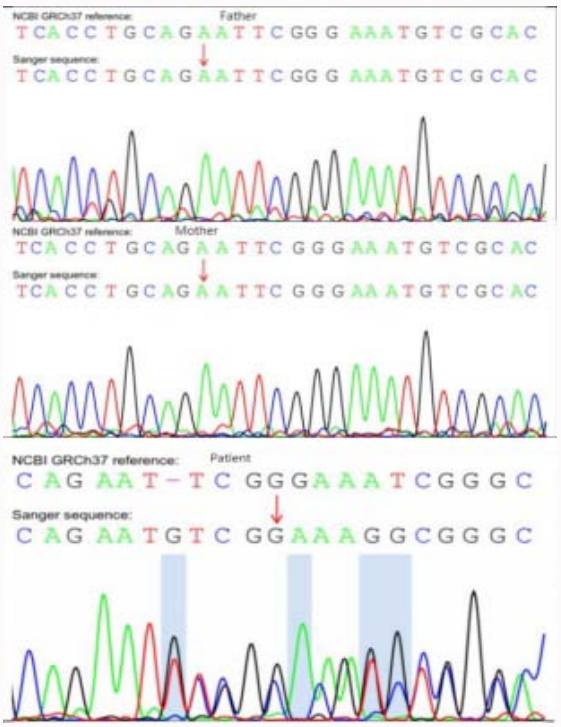

Figure 2: Genetic analysis of the PAX6 gene revealed 1 heterozygous mutation in this family. Arrows indicate the position of the mutation discuss.

composed of dense tactical photoreceptors. Histological studies revealed the foveal fossa appearing at fetal week 25 in association with progressive peripheral migration of retinal ganglion cells, inner plexuses and inner nuclear layers. After birth, the outer foveal core layer continues to thicken. The anatomy of the fovea at 15 to 45 months is similar to the fovea in adults [11,12]. When this process is interrupted, the fovea persists in the ganglion cells and the inner core layer. The OCT images showed multiple abnormal inner retinal layers preserved in the fovea [13]. And Thomas et al. [13,14] structural classification of macular foveal dysplasia: Grade 1 shallow pit, Outer Nuclear Layer (ONL) widening and photoreceptor Outer Segment (OS) lengthening; grade 2 without recess; grade 3 without OS break extension; and grade 4 without ONL widening. Grade 1 and 2 represent absent foveolar formation, complete conization, while grades 3 and 4 represent failure to conization.

PAX6 is a highly conserved transcription factor located in the long arm of human chromosome 11 at 13p (11p13), about 33 kb long, with 14 exons, and plays an important role in ocular development. The *PAX6* mutation causes genomic deletions and loss of adjacent upstream or downstream regulatory regions [15]. The clinical characterization was ocular abnormalities of varying severity, especially abnormalities in the anterior segment, including corneal opacity, cataract, and changes in the iris [16,17]. More than 600 different mutations in *PAX6* have been reported, and six have been reported to be associated with macular foveal dysplasia (Human Gene Mutation Database, 2019.3 http://portal.biobase-international.com/hgmd/pro/star/php),can be caused by hypomorphic missense mutations. In 1996, Azuma et al. found a heterozygous missense mutation in the *PAX6* gene (607108.0012). Heterozygous mutations in *PAX6* were reported in 1999 (607108.0014). Heterozygous splicing mutations identified in Vincent et *PAX6* in 2004 (607108.0021) [18]. In recent years, foreign scholars have suggested that macular foveal dysplasia may be more common than previously thought [19]. Only varying degrees of congenital nystagmus and poor vision, but probably no clinical characterization of aniridia or albinism, were defined as isolated macular foveal dysplasia [20].

In this study, in a child with FVH1, although strabismus was also a factor causing amblyopia, the corrected eye position after strabismus was horizontal and positive. After visual training, there was no significant improvement in vision. Therefore, the most important cause of weak vision is more closely related to macular dysplasia. The patient only had changes in the anterior segment of the sclera and cornea, and fundus examination revealed unclear structure of the macular fovea, which is consistent with the diagnosis of isolated macular fovea dysplasia. Through genetic testing of the proband in this family, a mutation in the *PAX6* gene c.127_135del was found. At the same time, direct sequencing of related gene variations was performed using first generation sequencing technology, and compared with the reference sequence, confirming that the mutation is a new mutation that has not yet been reported internationally. According to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG) gene mutation pathogenicity analysis standards and guidelines [11], the pathogenicity analysis of the PAX6 gene c.127_135del: p.Ser43-Ile45del heterozygous mutation is a non-frameshift mutation. Currently, this mutation site has not been included in Clinvar, and after consulting, there are no relevant literature reports. The mutation was found to comply with the pathogenic evidence PS2, PM2 supporting, and PM4 in the ACMG guidelines. The explanation is: 1) A newly discovered mutation that has been verified by both parents and has no family history; 2) Variations not found in the normal control population in ESP, 1000G, or EXAC databases; 3) Insertion/deletion or loss of termination codons within non repetitive regions leads to changes in protein length. The population frequency of this mutation site is low, and it is not included in the gnomAD_exome-EAS database.

Isolated macular foveal dysplasia is missed due to lack of associated ocular features, poor vision or nystagmus. The SD-OCT images can help to detect subtle signs of macular foveal dysplasia. We report that the macular fovea is grade 2 without foveal pit, that is, there are almost no normal pit indicators, but only low vision appears. To our knowledge, in previous reports, macular foveal dysplasia is often accompanied by severe low visual acuity, while visual acuity >0.3 is rare. In recent years, there have been reports of macular foveal dysplasia but good vision (Table 1) [11,12]. In previous visual studies, there are differences between macular morphological changes and visual development. The maturation of cone photoreceptors during macular foveal development is an independent phenomenon. Normal cone pooling was also observed in the absence of the macular fovea. This suggests that pit formation may not be required for cone development in the foveal region. This may explain the isolated macular foveal dysplasia with better vision.

Conclusion

In conclusion, our results again suggest that eyes with PAX6 mutations may be associated with rather good vision. As mild foveal dysplasia may be difficult to detect, confirming these subtle clinical findings, SD-OCT observing foveal structures can assist the diagnosis. With the necessary whole exon sequencing, it is helpful to detect gene mutations causing FVH 1 and make clear diagnosis. But further studies are still needed in the future to determine the

frequency of these clinical features and to determine what role they play in the diagnosis.

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