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Blue Cone Monochromacy Causes Deterioration in Visual Acuity and Color Vision in a Boy

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Abstract

Purpose: To present the genetic cause of progressive deterioration in visual acuity and color vision in a child with high myopia and strabismus. Here we describe a novel x-linked mutation in the opsin 1 medium-wave-sensitive (OPN1MW) gene in a child, leading to cone rod dystrophy.

Setting/Venue: Trio whole-exome sequencing (WES).

Methods: We reviewed the clinical data and eye exams including family history since the patient's first visit 2008. Further evaluation included fundus photography, optical coherence tomography and electroretinography. The child was also referred to neurological assessment and magnetic resonance imaging was performed. Genetic evaluation included the extraction of DNA from peripheral blood leukocytes, trio WES and bioinformatics analysis using the Burrows-Wheeler Aligner (BWA) and the Genome Analysis Tool Kit (GATK) software.

Results: A normal eye examination showed that the parents and brothers were healthy. The boy had bilateral impaired vision (best visual corrected 1/24), high myopia (BE -7.0 diopter) and esotropia. On fundus exam, normal fundus appearance was reported with only mild temporal pallor of the optic discs. Retinal thickness measured by optical coherence tomography was within normal limits. Electrophysiological studies were unspecified for cone rod dystrophy based on photopic and scotopic responses. The complete neurology examination and neuroimaging were normal. WES revealed no compound heterozygosity or recessive mutations.

Conclusions: Here we described a boy with severely impaired vision, not explained by the high myopia or the strabismus, who also had a progressive course. The family history was negative. Genetic evaluation revealed a deletion of exon 5 in the OPN1MW gene. He was diagnosed with a blue cone monochromacy. This child is a representative case with the common symptoms that are sometimes under-diagnosed without genetic evaluation.

Keywords: Color blindness; Blue cone monochromatism; Cone rod dystrophy

Abbreviations BCM: Blue Cone Monochromatism; BWA: Burrows-Wheeler Aligner; CRD: Cone Rod Dystrophy; ERG: Electroretinography; GATK: Genome Analysis Toolkit; WES: Whole-Exome Sequencing

Introduction

Myopia and strabismus are common in children and are associated with impaired vision [1-3]. However, refractive correction and treatment to prevent amblyopia usually overcome this impairment. When the usual treatment fails to improve vision, or when the child's vision further deteriorates, other causes for visual impairment should be investigated.

Degenerative retinal diseases are diagnosed in the presence of family history or during the first 2-4 decades [4,5]. Abnormal retinal hyperpigmentation and degenerative signs are the most common clues for this diagnosis. However, there is not always an abnormal fundus appearance [4]. Cone rod dystrophy (CRD) is a very prevalent retinal dystrophy [6]. Although all 3 modes of inheritance are possible, the most common is the recessive inheritance, especially in the presence of consanguinities or sick relatives. The autosomal recessive childhood-onset retinal dystrophies are a heterogeneous group of diseases affecting rods and cones, usually with late onset [7,8]. The prevalence of CRD is about 1/40,000, characterized by primary cone involvement or concomitant loss of both cones and rods [4]. Several genes such as ABCA4, ADAM9, CERKL, CNGA3, RDH5, RPGRIP1, TTLL5AIPL1, CRX, GUCA1A, GUCY2D, are specifically associated with CRD [4,9].

Herein, we present a patient without any family history, who had progressive visual deterioration in the presence of progressive high myopia and strabismus, with impaired color vision, who was found to

carry a de novo novel opsin 1 (cone pigments) medium-wave-sensitive (OPN1MW) mutation.

Case Presentation

A 10-year-old boy was monitored in our Pediatric Ophthalmology Unit from 2008 to 2015 because of impaired vision and strabismus. The parents were not related and there was no family history of eye disease. The boy has three healthy brothers, aged 15, 13, and 9 years of age.

His best corrected visual acuity deteriorated to 1/36 in each eye since diagnosis. Refraction showed high myopia (-7.5 D sphere each eye). The Ishihara color plate text exam revealed no color vision (0/10) in each eye. He had esotropia (exceeded from 10PD to 40PD before operation was performed). While the fundus exam did not show any degenerative retinal changes, only a mild temporal pallor of the discs was detected without attenuation of the retinal vessels (Figure 1). Retinal thickness measured by optical coherence tomography was within normal limits (Figure 2). The neurological exam including magnetic resonance imaging was normal. His full-field rod-cone electroretinogram (ERG) was positive for CRD. Farnsworth D-15 dichotomous color blindness test on March 2016 showed multiple errors in each eye but no clear axis could be recognized. Berson's specific color test for blue cone monochromatism (BCM) was not available for examination.

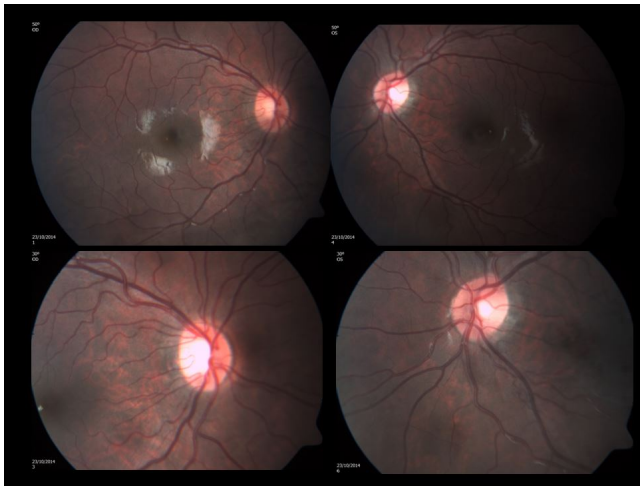

Figure 1: Fundus photos of the child. Upper line lower magnification of right and left eyes. Lower line, higher magnification. Note the lack of degenerative signs.

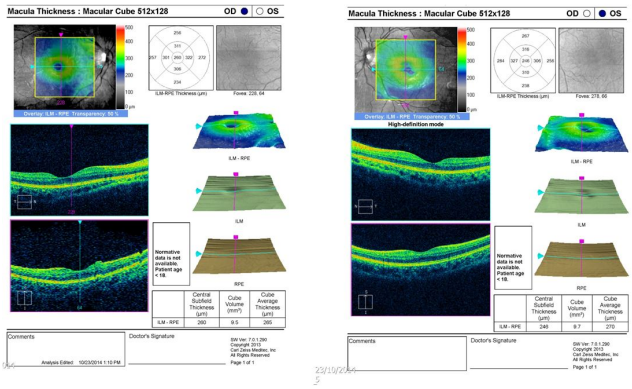

Figure 2: OCT exam of both retinae. Note the normal thickness and structure of the macula of both eyes.

Methods

Blood sample and DNA extraction: Blood samples were collected following the written informed consent under local and national ethical committee's approval. Genomic DNA was extracted from peripheral blood leukocytes using iPrep™ Purification Instrument (Life Technologies, Invitrogen Grand Island, NY, USA) and iPrep™ PureLink® gDNA blood kit (Invitrogen), according to the manufacturer's instructions.

Whole exome sequencing (WES): Trio whole exome sequencing (Gene by Gene LTD, Houston, Texas, USA) analysis was performed using Nextera kit (Illumina LTD.) and were sequenced by the Illumina HiSeq sequencing platform.

Bioinformatics analysis: Bioinformatics analysis was performed using the Burrows-Wheeler Aligner (BWA) tool for mapping reads to the human genome and Genome Analysis Toolkit (GATK) or ANNOVAR softwares for variant discovery. Bioinformatics analysis was performed with the Burrows-Wheeler Aligner (BWA) software [PMID 19451168] for mapping reads to the human genome (hg19 version), followed with the GATK [PMID 2543163, 21478889, 20644199]: a software package for analysis of high-throughput sequencing data and variant discovery. Variant annotations were added using ANNOVAR [PMID 26379229, 22717648, 20601685]: a software tool to utilize update-to-date information to functionally annotate genetic variants detected.

Results

The WES results were filtered for single nucleotide polymorphisms mutations in known or unknown genes. Analysis for recessive or de novo single nucleotide polymorphisms did not reveal pathology.

In the next step, we used a new technique of coverage analysis in order to find large deletions. In this method, the WES of the patient is measured in comparison to the results of all patients examined in the same platform at the same time. A significant difference in the number of reads in the subject of interest and the other individuals may reveal a target of deletion (Figure 3). We detected a deletion of exon 5 (5/6) in OPN1MW gene (NM_000513.2) (Figure 4).

Figure 3: Coverage reads for exon 5 in OPN1MW gene. A. Affected boy. B. The mother of the affected boy. C-F. Other healthy individuals examined the same date for different reason. G. Reference genome, taken from IGV.

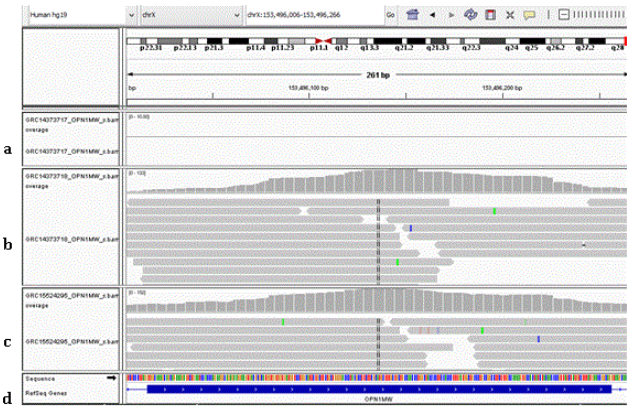

Figure 4: Coverage reads for exon 5 in OPN1MW gene of the family. A. Affected boy B. The mother. C. The father D. The reference gene, taken from IGV.

Discussion

We report a novel de novo exon deletion of OPN1MW in a 10-year-old child presenting with high myopia, impaired vision and strabismus. He did not have a family history of eye disease and his complaints and eye examination findings were not explained by simple myopia or strabismus/bilateral amblyopia.

OPN1MW encodes for the protein called green cone photopigment. This opsin pigment is more sensitive to light in the middle of the visible spectrum (yellow/green light). When OPN1MW gene mutations lead to completely nonfunctional M cones, color vision depends entirely on the other two types of cones. Therefore, a defective gene resulting from a total loss of M cone function generally causes deutanopic color blindness. The green and red color blindness are X linked and are inherited as anomalies by the mother. The blue cone defects generally are acquired by pathologies and other inner causes.

Genetic WES evaluation revealed BCM. This is a rare X-linked, recessive disorder characterized by markedly reduced vision, severe photophobia, congenital nystagmus, and inability to discriminate colors, caused by a loss-of-function of both the OPN1LW and OPN1MW opsin genes. The cone opsin gene cluster is composed of 2-9 paralogs with 99.8% sequence homology and is susceptible to deletions, duplications, and mutations [10]. Our patient had an exon 5 deletion in the OPN1LW and OPN1MW opsin genes. He is a very representative case, being male (an X-linked condition) with otherwise unexplained high myopia and reduced color vision. Although the deletion in this relevant gene was found on WES with comparison to normal patients, it is very difficult to validate the results using regular Sanger direct sequencing due to the high repetition of the gene cluster in this area [11].

In this study, we describe an otherwise healthy boy who needed spectacles to correct high myopia and was followed-up at the clinic. However, his best visual correction (BVA) remained as low as 1/24 each eye, not explained by simple bilateral amblyopia (due to refractive ametropia and strabismus). Lack of family history for degenerative eye disease delayed the investigation into the patient's genetic background. This might be the case in many children being seen in a Pediatric Ophthalmology Outpatient Clinic.

To date, with the improvement in diagnosis and genetic screening and better and cheaper methods available, ophthalmologists should use every available tool to solve unexplained reduced vision and keep in mind that genetics may play a role in the condition. Next generation sequencing is available and efficient while the Sanger technique fails to detect these areas. Whole exome sequencing utilizing a specific panel for the relevant genes and whole genome sequencing using the illumine hybridization technique are currently the most popular methods [12,13].

This case demonstrates how the use of a genetic tool improved the diagnosis of poor vision in a 10-year-old boy. Pathological ERG raised the suspicion of retinal degeneration. WES search with some manipulation of the data revealed the diagnosis of BCM. Surprisingly, the boy is typical for this disease. We highly recommend wide screening, ERG and WES for unexplained progressive myopia that is not completely corrected by spectacles, even in the case of no family history.

Awareness of the feasibility of these examinations and the possible influence on genetic treatment [14,15] should yield a better understanding of the importance of wider screening in the pediatric population with unexplained, or partially explained, impaired vision.

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