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Benign Yellow Dot Maculopathy

A New Macular Phenotype

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Purpose: To describe a novel macular phenotype that is associated with normal visual function.

Design: Retrospective, observational case series.

Participants: Thirty-six affected individuals from 23 unrelated families.

Methods: This was a retrospective study of patients who had a characteristic macular phenotype. Subjects underwent a full ocular examination, electrophysiologic studies, spectral-domain optical coherence tomography (OCT), and fundus autofluorescence imaging. Genomic analyses were performed using haplotype sharing analysis and whole-exome sequencing.

Main Outcome Measures: Visual acuity, retinal features, electroretinography, whole-exome sequencing.

Results: Twenty-six of 36 subjects were female. The median age of subjects at presentation was 15 years (range, 5–59 years). The majority of subjects were asymptomatic and presented after a routine eye examination (22/36 subjects) or after screening because of a positive family history (13/36 subjects) or by another ophthalmologist (1/36 subjects). Of the 3 symptomatic subjects, 2 had reduced visual acuity secondary to nonorganic visual loss and bilateral ametropic amblyopia with strabismus. Visual acuity was 0.18 logarithm of the minimum angle of resolution (logMAR) or better in 30 of 33 subjects. Color vision was normal in all subjects tested, except for the subject with nonorganic visual loss. All subjects had bilateral symmetric multiple yellow dots at the macula. In the majority of subjects, these were evenly distributed throughout the fovea, but in 9 subjects they were concentrated in the nasal parafoveal area. The dots were hyperautofluorescent on fundus autofluorescence imaging. The OCT imaging was generally normal, but in 6 subjects subtle irregularities at the inner segment ellipsoid band were seen. Electrophysiologic studies identified normal macular function in 17 of 19 subjects and normal full-field retinal function in all subjects. Whole-exome analysis across 3 unrelated families found no pathogenic variants in known macular dystrophy genes. Haplotype sharing analysis in 1 family excluded linkage with the North Carolina macular dystrophy (MCDR1) locus.

Conclusions: A new retinal phenotype is described, which is characterized by bilateral multiple early-onset yellow dots at the macula. Visual function is normal, and the condition is nonprogressive. In familial cases, the phenotype seems to be inherited in an autosomal dominant manner, but a causative gene is yet to be ascertained. *Ophthalmology 2017;■:1–10* © *2017 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

The inherited macular dystrophies are a clinically and genetically heterogeneous group of disorders in which there are structural and functional abnormalities of the central retina.[1,2] These disorders usually occur in isolation, but they may be associated with a variety of systemic abnormalities. All of the Mendelian and mitochondrial inheritance patterns have been described.[3] Most forms of macular dystrophy present in later childhood or in adult life after a period of normal visual development, and they are usually progressive. The exception is a rare group of disorders that present with visual impairment in infancy and in which there is abnormal foveal or macular development.[4] Such disorders do not commonly progress.

Although most macular dystrophies present with central visual loss, some patients with normal visual acuity are referred to ophthalmologists when a macular abnormality is noted on routine optometric examination. Whatever the mode of presentation, the specific diagnosis is made on the basis of the macular appearance, along with retinal imaging, electrophysiologic studies, inheritance patterns, and, increasingly, the results of molecular genetic testing.[5] Some clinical phenotypes do not easily fit into well-characterized disorders.

The present report describes a novel, nonprogressive, macular phenotype, that may occur in isolation or as a familial trait, and that is associated with normal visual function.

http://dx.doi.org/10.1016/j.ophtha.2017.02.026
ISSN 0161-6420/17

Methods

Subjects

Subjects were ascertained on the basis of the presence of a specific macular phenotype and were recruited from the pediatric and adult medical retina clinics of 3 ophthalmologists (1 from the United Kingdom and 2 from the United States). Informed consent was obtained from all subjects and family members involved in this study. The study had institutional review board approval from Cincinnati Children's Hospital, Bascom Palmer Eye Hospital, and the Moorfields Eye Hospital Local Research Ethics Committee, and all investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Clinical Examination

Best-corrected monocular visual acuity was measured using a logarithm of the minimum angle of resolution (logMAR) scale, and color vision was assessed using Ishihara pseudoisochromatic plates, Hardy Rand Rittler color plates, and the Farnsworth-Munsell 100 Hue Test. Funduscopy and slit-lamp biomicroscopy were performed. Color fundus photography was undertaken in all subjects; in the majority, this was carried out using a Topcon TRC 501A retinal camera (Topcon Corporation, Tokyo, Japan), but in some individuals, seen early in the study period, a Zeiss (Oberkochen, Germany) retinal film camera was used. Spectral-domain optical coherence tomography (OCT) using a Heidelberg Spectralis spectral-domain OCT scanner (Heidelberg Engineering, Dossenheim, Germany) and fundus autofluorescence imaging (Heidelberg Engineering) also were performed. Electrophysiologic assessment including full-field electroretinography (ERG), pattern electroretinography (PERG), and electro-oculograms (EOGs) were performed in the subjects from the United Kingdom according to the recommendations of the International Society for Clinical Electrophysiology of Vision.[6–8] Fundus fluorescein angiography was also undertaken in certain subjects.

Genomic Analyses

DNA was extracted from whole blood by standard methods. Whole-exome sequencing was performed for: family 4 (subjects 8, 9, and 11), Moorfields Eye Hospital Genetic Clinic number GC14302; family 8 (subjects 19, 20, and 21); and family 22 (subject 35), as previously described.[9] Briefly, double-stranded DNA was sheared by sonication to an average size of 200 base pairs. After 9 cycles of polymerase chain reaction amplification using the Clontech Advantage II kit (Takara Bio USA, Mountain View, CA), 1 μg of genomic library was recovered for exome enrichment using the NimbleGen EZ Exome V2 kit (Roche Sequencing, Pleasanton, CA). Libraries were sequenced on an Illumina HiSeq2500 (Illumina, Inc, San Diego, CA). Data analysis used the Broad Institute's Genome Analysis Toolkit.[10] Reads were aligned with the Illumina Chastity Filter with the Burrows Wheeler Aligner.[11] Variant sites were called using the Genome Analysis Toolkit UnifiedGenotyper module.[10] Variant filtering and group analysis were performed using Qiagen Ingenuity Variant Analysis (Hilden, Germany).

Haplotype sharing analysis was performed on single nucleotide polymorphism (SNP) data from 5 affected members of family 4 genotyped using the Illumina HumanOmniExpress-24 v1.0 beadchip (Illumina, Inc) that includes >715 000 SNPs. Genotypes were determined using the Genotyping Module in the Illumina GenomeStudio v2011.1 software. Build hg19/GRCh37 was used to annotate chromosomal coordinates. The haplotype sharing analysis was carried out using the nonparametric homozygosity haplotype (HH) method that searches for chromosomal segments sharing the same haplotype across affected individuals (as an indication of genetic linkage with the disease).[12] The HH is a type of haplotype described by the homozygous SNPs only (all heterozygous SNPs are removed). Because affected family members who inherited the same mutation from a common ancestor share a chromosomal segment identical-by-descent (IBD) around the disease gene, they should not have discordant homozygous calls in the IBD region, and thus they should share the same HH. The HH approach predicts IBD regions through the identification of regions with a conserved HH defined as those regions with a shared HH among patients and a genetic length longer than a certain cutoff value (recommended cutoff for Illumina array is 2.5/3.0 cM).

Results

A total of 36 affected individuals were identified from 23 unrelated families. Subjects were referred from community optometrists (22/36), from another ophthalmologist (1/36), or after screening because of a positive family history (13/36). Of the 36 subjects, 15 were sporadic. A total of 12 of the 15 sporadic cases were white, 1 was of West African origin, 1 was of South Asian descent, and 1 was of African-Caribbean descent. Eight families (all white) demonstrated an autosomal dominant inheritance pattern (Fig 1, pedigrees of affected families that underwent genomic analysis). The median age at presentation was 15 years (range, 5–59 years). Twenty-six of 36 subjects were female (Table 1).

Thirty-three subjects (91.7%) were asymptomatic. One subject experienced floaters (subject 35) but had normal visual acuities and a normal peripheral retinal examination. Reduced visual acuity was the presenting symptom in the other 2 symptomatic subjects (subjects 8 and 23). No cause was found for the reduced vision in subject 8, who presented at age 16 years and in whom multiple electrophysiologic studies over a number of years were normal. A diagnosis of nonorganic visual loss was made. Subject 23 presented to another ophthalmologist at age 4 years with reduced vision, attributed to bilateral ametropic amblyopia due to hypermetropic astigmatism; macular yellow dots were not identified until age 6 years. His vision eventually improved with refractive correction and occlusion therapy to 0.18 in the right eye and 0.26 in the left eye.

Refractive error (identified in 15 subjects) was the predominant finding in the 17 subjects who had any ocular history (Table 1). Two of 17 subjects had been treated for strabismus, and 3 of 17 subjects had been treated for amblyopia. One subject developed spontaneously resolving bilateral optic neuropathy of unknown cause during the follow-up period, 4.5 years after presentation with the macular phenotype, and 1 subject had nonorganic visual loss. General health was good in all, except for subject 33, who was taking antidepressants.

Visual acuity at presentation was 0.18 logMAR or better in both eyes in 30 of 33 subjects (Table 1). In 3 subjects, the visual acuity was unrecorded (these were all affected family members of probands). Subject 8, with nonorganic visual loss, had a presenting visual acuity of 0.78 logMAR in either eye. Amblyopia affected subjects 23 (bilateral), 27 (unilateral right eye), and 28 (unilateral left eye) (Table 1). Successful amblyopia therapy improved the acuity in subject 28 to better than 0.18 logMAR in both eyes. The finding of amblyopia and refractive error in a subset of patients likely reflects the fact that the