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Case Report

Familial Optic Disc Pits in 2 Father-Son Pairs: Clinical Features and Genetic Analysis

Devin Betsch[a] Andrew Orr[a, b] Mathew Nightingale[b] Daniel Gaston[b] Rishi Gupta[a]

[a]Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax, NS, Canada; [b]Department of Pathology, Dalhousie University, Halifax, NS, Canada

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Abstract
Congenital optic disc pits (ODPs) are well-circumscribed depressions within the optic disc. Thought to arise from anomalous closure of the optic fissure during embryonic development, they are now considered to lie on a broader spectrum of congenital optic disc anomaly (CODA). An increasing number of reports describe clustering of these cases within families, suggesting that inherited genetic elements play a role in disease predisposition. Here, we highlight the clinical features of 2 sets of father-son pairs affected with ODPs and provide preliminary molecular genetic analysis. Subjects underwent complete ophthalmological examination and imaging. In addition, whole-exome sequencing was carried out following informed consent. The resulting datasets were examined for potentially causal genetic variants, both in genes already known to be linked to CODA as well as those likely to lie in the same or similar genetic pathways. In this instance, no unambiguously causal variants were identified. This case series highlights the familial inheritance of ODPs, adding to the existing body of literature supporting an underlying genetic cause for this rare clinical entity. The inclusion here of specific molecular findings raises the hope that the genetic pathophysiology underlying rare entities like ODPs might be clarified in the future by the addition of similarly molecular-documented reports.

Note that D.B. and A.O. share first authorship.

Correspondence to:
Devin Betsch, dv307044@dal.ca

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Introduction

Congenital optic disc pits (ODPs) are well-circumscribed depressions within the optic disc thought to arise from anomalous closure of the optic fissure during embryonic development [1, 2]. These are rare clinical entities, occurring at a rate of about 1:11,000 [3], and are not to be confused with acquired pits of the optic nerve encountered in the setting of primary open-angle glaucoma and pathologic myopia [4]. A study by Ohno-Matsui et al. [5] demonstrated that pit-like clefts of the optic nerve or adjacent scleral crescent were found in 16.2% of highly myopic eyes.

Until recently, ODPs were thought to be distinct from other congenital malformations of the optic nerve like coloboma and morning glory disc anomaly. An increasing body of evidence now suggests that these disease processes occur on a spectrum, organized collectively under the title of congenital optic disc anomaly (CODA) [6]. Furthermore, while the majority of CODAs arise sporadically, there are a number of reports describing clustering of CODA within families, usually segregating as an autosomal dominant trait with variable penetrance [7], suggesting that inherited genetic variation plays a causal role [6, 7]. For the most part, however, the components of this genetic variation remain obscure.

A number of strategies have been employed in the search for the genetic variation underlying CODAs. Screening of candidate genes known to be associated with ocular malformation, such as PAX2 (oculorenal syndrome), PAX3 (Waardenburg Type 3), PAX6 (aniridia), SHH (ocular coloboma), MITF (Waardenburg Type 1 and 2), and MIR204 (familial colobomas with retinal dystrophy) have thus far been unrewarding [4, 7–10]. In a significant advance, however, Fingert et al. [7] established linkage to chromosome 12q in a pedigree-based multipoint approach using 17 family members affected with an array of cavitary disc anomalies. Initial testing of potential candidate genes within this interval, including GDF-11, NEUROD4, and WIF1, yielded negative results. However, a follow-up paper on the same patient cohort revealed a causal 6 kpb heterozygous triplication implicated in transcription enhancement upstream of the matrix metalloproteinase 19 (MMP19) gene in all affected family members [11]. In a separate development, Wang et al. [10] used whole-exome sequencing to identify another new genetic locus for CODA on chromosome 14q12q22.1.

In this report, we highlight 2 sets of father-son pairs with ODPs in order to further study and characterize specific genes of interest in familial ODPs. As this is a rare clinical entity, we believe reporting findings, even on a small number of family members, is a potentially helpful addition to the existing literature. In particular, it may be of use to researchers, health-care providers, and patients in the future, in order to identify those at risk of either developing ODP themselves or passing relevant gene(s) on to offspring. This knowledge could lead to improved surveillance of families known to carry at-risk genetic variants. More broadly, it offers the tantalizing prospect of improving our understanding, at the most basic level, of the genetic pathways underlying normal optic nerve development. Ultimately, better therapies, rationally designed to address specific molecular targets, might result.

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Son A, an otherwise healthy 19-year-old, was found to have a visual acuity of 6/6 in the right eye, and 6/7.5 in the left, with normal IOP bilaterally. Dilated exam revealed a normal fundus and optic nerve in the right eye, and an ODP with subretinal and intraretinal fluid in the left, which was confirmed on SD-OCT (shown in Fig. 1). The central vision in his left eye continued to decline (6/9) with observation, and he was thus treated with pars plana vitrectomy, elevation of the hyaloid, removal of glial tissue from the ODP, fluid-air exchange,

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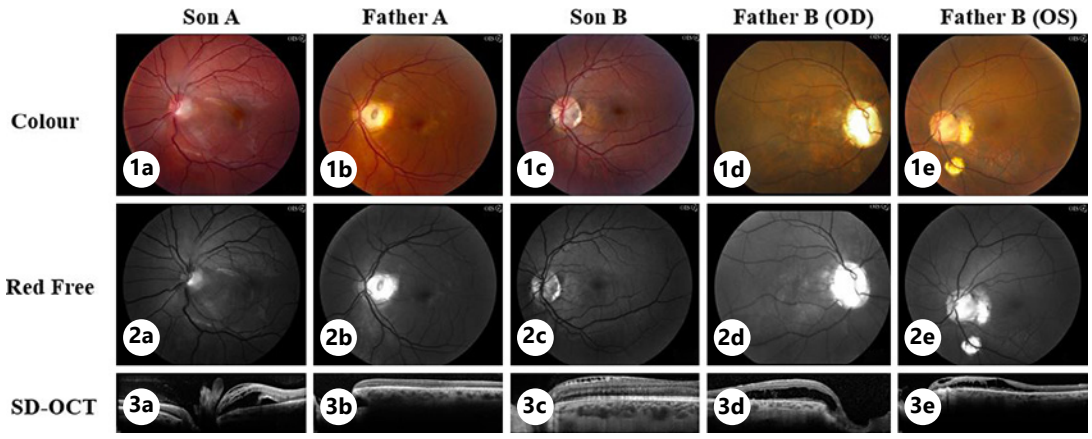

Fig. 1. Color, red-free, and SD-OCT images of each participants' ODP. Son A's fundus photos of the left eye (**1a**, **2a**) show a temporal ODP, as well as fluid tracking into the macula. This is confirmed on SD-OCT (**3a**), which shows both subretinal and intraretinal fluid in the macula, as well as glial tissue emanating from the ODP. Father A's fundus photos of the left eye (**1b**, **2b**) show a well-circumscribed temporal ODP. This was confirmed on his SD-OCT, which also shows areas of attenuation of the ellipsoid zone (**3b**). Son B's fundus photos of the left eye (**1c**, **2c**) show a temporal ODP. His SD-OCT (**3c**) shows a very mild amount of inner retinal schisis. Father B's fundus photos of the right eye (**1d**, **2d**) show a temporal ODP, and his SD-OCT shows adjacent subretinal fluid (**3d**). Father B's fundus photos of the left eye (**1e**, **2e**) show a temporal ODP and well-circumscribed foci of retinal atrophy temporal to the disc and along the inferior arcade, and his SD-OCT (**3e**) shows an ODP, as well as adjacent subretinal and intraretinal fluid. ODP, optic disc pit.

and instillation of SF6 gas. At 14-month post-surgery, his visual acuity measured 6/7.5, with resolution of ODP maculopathy.

Father A, an otherwise healthy 58-year-old, had previously been known to have a symptomatic left ODP, which had spontaneously resolved. His visual acuity was 6/6 bilaterally, and his IOP was normal in both eyes. Dilated exam showed a normal optic nerve in the right eye and an ODP in the left eye. His SD-OCT showed no evidence of cystoid macular edema or subretinal fluid but did demonstrate attenuation of the ellipsoid zone in the left eye (shown in Fig. 1).

Son B, an otherwise healthy 23-year-old, was found to have a visual acuity of 6/6 in the right eye, and 6/9 in the left, with normal IOP bilaterally. Dilated exam revealed a left ODP, and his SD-OCT revealed mild inner retinal schisis (shown in Fig. 1). SD-OCT also confirmed anatomical continuity between the ODP and schitic changes. His right optic nerve was normal. He continues to be followed on a yearly basis and remains asymptomatic. His most recent visual acuity was 6/6 in the right eye and 6/7.5 in the left.

Father B, a 68-year-old male with a history of Type 2 diabetes, hypertension, and dyslipidemia was found to have a visual acuity of 6/120 in the right eye, and 6/9 in the left, with normal IOP bilaterally. Slit-lamp and dilated fundus exam revealed a 4+ nuclear sclerotic cataract on the right, bilateral ODPs, and inferior retinal colobomas. OCT showed ODPs and intraretinal fluid within the macula bilaterally (shown in Fig. 1). He underwent right eye phacoemulsification and intraocular lens implantation, as well as pars plana vitrectomy, elevation of the hyaloid, endolaser photocoagulation around the inferior coloboma, fluid-air exchange, and instillation of SF6 gas. Post-operatively, his visual acuity on that side improved to 6/60 with a well-centered intraocular lens and decreased amounts of subretinal and intraretinal fluid demonstrated on follow-up imaging. The left eye ODP maculopathy has remained stable for years and, given his good vision and a lack of symptoms, the patient has chosen observation over intervention.

All 4 affected individuals underwent whole-exome sequencing carried out on an Illumina HiSeq sequencing instrument using DNA extracted by standard techniques from peripheral blood samples. Raw sequencing data (FastQ files) were quality checked using FastQC and paired-end sequencing reads mapped to the human reference genome (GRCh37) using BWA-MEM.

Data were processed using the current recommended Best Practices workflow and the Genome Analysis Toolkit suite from the Broad Institute with single-nucleotide variants and small insertion/deletion variants using the GATK HaplotypeCaller. All single-nucleotide variants and insertion/deletions were annotated using a combination of snpEff (a variant annotation and effect prediction tool) and GEMINI (GEnome MINIng, a flexible software package for exploring all forms of human genetic variation). The database functions of GEMINI were then used to select variants that pass standard filtering protocols for rare diseases (minor allele frequency of <0.05% in any population from the 1,000 Genomes, Exome Aggregation Consortium, or Exome Sequencing Project datasets). Several bioinformatics programs for the detection of structural and copy-number variants were used, including Manta and Canvas, both produced by Illumina, Inc., and included in their standard workflows.

As expected, the exome sequencing dataset revealed a large number of potentially deleterious variants in all 4 affected samples. Analysis of these data was carried in the following manner:

First, the coding sequences of the following candidate genes linked to optic nerve anomalies were evaluated: PAX6 (MIM: 607108), PAX2 (MIM: 167409), and MMP19 (MIM: 601807). No mutations were present in any of the 4 samples.

Following this, variants not shared by the respective affected parent-offspring pairs – that is, those inconsistent with the hypothesis that a causal variant had been passed from father to son – were excluded. Those remaining were then filtered to include only the following likely pathogenic entities: insertions, deletions, frameshift, splice-site, and predicted damaging missense changes. At the end of this process, 368 and 289 variants, respectively, were left as potential candidates in the Son A/Father A and Son B/Father B families.

Within these 2 variant pools, associated genes were ranked according to their likelihood to fit within pathways already known to be associated with optic nerve malformations, a prioritization established by a human phenotype ontology search (https://hpo.jax.org/app/) using the following seed terms: morning glory anomaly HP.0025514, cavitary optic disc anomalies OMIM:611543, and optic nerve coloboma HP:0000588. The top 5 candidates in each of the 2 families and the associated variants are listed in Table 1. None were shared between the 2 families. Their relationship to the CODA phenotype remains unknown. Table 2 shows the predicted effect of each of the top 5 variants on overall protein function. The majority were found to be damaging or disease causing.

All 4 patients included in this study were found to have ODPs. Through patient interviews, pedigrees were constructed for both participating families (shown in Fig. 2). Those individuals included in our study were the only known affected family members with ODPs. Although we did not specifically examine other family members, it is possible that others harbored similar optic disc findings with asymptomatic disease. Previously published case reports and case series on the topic of familial ODPs have suggested an autosomal dominant pattern of inheritance, which could be consistent with the inheritance demonstrated in our participants [10].

Presentation varied among the 4 individuals included in the study. Two of the 4 (Father A and Son B) were asymptomatic at the time of their initial ocular examination at our Eye Care Center. Son A and Father B required surgical intervention for repair of ODP-related maculopathy. Of note, there are several treatment strategies available for this

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Table 1. List of the 5 most common genetic variants associated with relevant HPO terms

Top 5 gene variants seen in Family A				
1	IGSF9	Immunoglobulin superfamily, member 9	c.862_865delCTGC	p.Leu288fs
2	MPP4	Membrane protein, palmitoylated 4	c.869G>A	p.Arg290Gln
3	SDHA	Succinate dehydrogenase complex, subunit A, flavoprotein	c.1942A>C	p.Thr648Pro
4	LPP	Lim domain-containing preferred translocation partner in lipoma	c.1409T>A	p.Ile470Asn
5	RXFP1	Relaxin/insulin-like family peptide receptor 1	c.1771G>A	p.Ala591Thr
Top 5 gene variants seen in Family B				
1	HMCN1	Hemicentin	c.14122A>C	p.Ser4708Arg
2	SCN3A	Sodium voltage-gated channel, alpha subunit 3	c.3685T>C	p.Tyr1229His
3	SLC6A12	Solute carrier family 6 (neurotransmitter transporter, betaine/gaba), member 12	c.1424T>G	p.Val475Gly
4	SORBS2	Sorbin and SH3 domains-containing protein	c.365G>A	p.Ser122Asn
5	ZNF398	Zinc finger protein 398	c.1364C>T	p.Ala455Val

This table lists the top 5 candidates in each of the 2 families and the associated variants, after being ranked according to their likelihood to fit within pathways already known to be associated with optic nerve malformations. This prioritization was established by a HPO search (https://hpo.jax.org/app/) using the following seed terms: morning glory anomaly HP.0025514, cavitary optic disc anomalies OMIM:611543, and optic nerve coloboma HP:0000588. HPO, human phenotype ontology.

clinical entity, including but not limited to systemic medications such as steroid and acetazolamide, peripapillary laser, gas injection, and macular buckling. Vitrectomy has been tried with various surgical adjuncts, including hyaloid separation, removal of vitreous strands from the pit, inverting an ILM flap over the pit, filling the pit with ILM, and inner retinal fenestration. Intrafamilial phenotypic variation, as seen with our cases, has previously been demonstrated in a large, 4 generation pedigree published by Wang et al. [10]. All participants had unilateral ODPs, with the exception of Father B. Most often, ODPs are incidental, unilateral findings on routine eye examination, with only about 15% of cases being bilateral [2]. Given that this clinical entity is often asymptomatic, it seems reasonable to assume that cases of ODPs are likely underreported in the literature, making study of this entity all the more challenging.

After cross-referencing our whole-exome sequencing data for each family against the human phenome ontology terms for CODA, morning glory anomaly, and optic nerve coloboma, we generated lists of the 5 most common genes and associated variants for each family (shown in Table 1). None of these variants were shared by the 2 families, and it is important to note that their significance, if any, remains unknown.

Conclusion

Many genetically predisposed conditions are rare enough that no one clinical center can gather enough cases to enable a deeper understanding of their molecular origins. Progress thus depends on collaborative efforts involving the contribution of multiple groups. In some areas, formal disease-focused consortia (for instance, in exfoliation syndrome) have engendered notable advances based on clinical collections of many thousands of affected cases and a similar number of controls [12]. The majority of diseases lack these types of organized

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Table 2. Predicted effects of the 5 most common genetic variants on protein function

	Provean		SIFT		MutationTaster		
	prediction	score	prediction	score	prediction	accuracy	gerp score
Top 5 gene variants seen in Family A							
IGSF9 c.862_865delCTGC p.Leu288fs	–	–	–	–	–	–	–
MPP4 c.869G>A p.Arg290Gln	Neutral	−2.206	Damaging	0.021	Disease causing	0.9999	5.4499
SDHA c.1942A>C p.Thr648Pro	Deleterious	−4.75	Damaging	0.034	Disease causing	0.9999	4.1199
LPP c.1409T>A p.Ile470Asn	Deleterious	−5.47	Damaging	0.033	Disease causing	1	6.17
RXFP1 c.1771G>A p.Ala591Thr	Deleterious	−3.26	Damaging	0.016	Disease causing	1	5.69
Top 5 gene variants seen in Family B							
HMCN1 c.14122A>C p.Ser4708Arg	Neutral	−1.55	Damaging	0.012	Disease causing	0.9997	5.82
SCN3A c.3685T>C p.Tyr1229His	Damaging	−4.73	Damaging	0	Disease causing	0.9999	5.88
SLC6A12 c.1424T>G p.Val475Gly	Deleterious	−6.23	Tolerated	0.128	Disease causing	1	4.03
SORBS2 c.365G>A p.Ser122Asn	Neutral	−1.404	Damaging	0.11	Disease causing	0.9981	5.51
ZNF398 c.1364C>T p.Ala455Val	Neutral	−1.098	Tolerated	0.153	Disease causing	0.5244	4.6599

This table lists the 5 most common genetic variants in each of the 2 families, as well as their predicted effects on overall protein function. Three different software programs were used for these predictions: Provean, SIFT, and MutationTaster.

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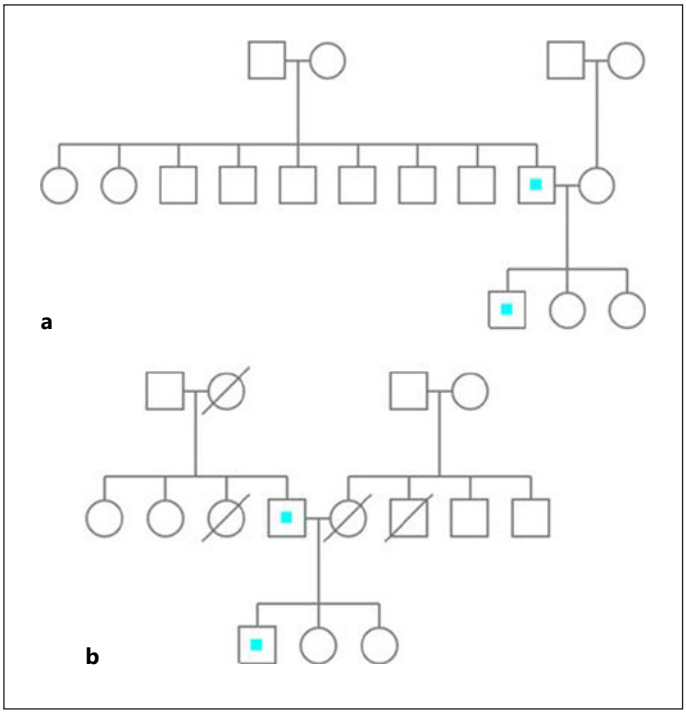

Fig. 2. Three generation pedigrees for Family A and B showing those affected with ODPs. The pedigrees of Family A (**a**) and B (**b**) are shown, with individuals known to have a diagnosis of ODP indicated by a blue square. Each family contains a single father-son pair with known ODPs. ODP, optic disc pit.

consortia, however. In this context, molecularly documented case reports like this one might, collectively, represent an opportunity for progress, even though no unambiguously causal variants were identified by us. By integrating clinical and molecular findings, we hope both to educate clinicians and contribute genetic data that may, eventually, be pooled to provide a deeper understanding of the developmental pathways underlying optic nerve development. Finally, although further research is clearly required in this area, the increasing number of published cases of ODPs occurring within families continues to support an underlying genetic basis for this rare and interesting ophthalmologic entity.

Acknowledgement

We would like to thank the patients included in the report for participating in this research.

Statement of Ethics

Written informed consent was obtained from all patients for publication of this case report and any accompanying images. Consent was also obtained for whole-exome sequencing and study participation. This study protocol was approved by our institute's committee on human research (ROMEO #1011873).

Conflict of Interest Statement

D.B., A.O., M.N., D.G., and R.R.G. have no conflicts of interest to disclose.

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Author Contributions

Note that D.B. and A.O. share first authorship. D.B. conducted the literature review, chart review, and participant interviews, coordinated whole-exome sequencing, and wrote and prepared the manuscript for submission. A.O. completed the REB approval process, assisted in literature review, manuscript writing, and editing, and provided expertise on genetic sequencing and data analysis. M.N. and D.G. coordinated and analyzed the whole-exome sequencing data and assisted in writing this portion of the manuscript. R.R.G. recruited patients, assisted in literature review, manuscript writing, and submission, and provided expertise on ODPs, as well as imaging.

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