Microphthalmia, Anophthalmia, and Coloboma and Associated Ocular and Systemic Features
Understanding the Spectrum

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IMPORTANCE Microphthalmia, anophthalmia, and coloboma form an interrelated spectrum of congenital eye abnormalities.

OBJECTIVE To document the ocular and systemic findings and inheritance patterns in patients with microphthalmia, anophthalmia, and coloboma disease to gain insight into the underlying developmental etiologies.

DESIGN, SETTING, AND PARTICIPANTS This retrospective consecutive case series was conducted at a tertiary referral center. Included in the study were 141 patients with microphthalmia, anophthalmia, and coloboma disease without a recognized syndromic etiology who attended the Westmead Children's Hospital, Sydney, from 1981-2012.

EXPOSURE Cases were grouped on the basis of the presence or absence of an optic fissure closure defect (OFCD); those with OFCD were further subdivided into microphthalmic and nonmicrophthalmic cases. Anophthalmic cases were considered as a separate group.

MAIN OUTCOMES AND MEASURES Associated ocular and systemic abnormalities and inheritance patterns were assessed.

RESULTS Of 141 cases, 61 (43%) were microphthalmic non-OFCD (NOFCD), 34 (24%) microphthalmic OFCD, 32 (23%) nonmicrophthalmic coloboma (OFCD), 9 (6%) anophthalmic, and 5 (4%) were unclassified. Sixty-three (45%) had bilateral disease. Eighty-four patients (60%) had an associated ocular abnormality; of these, cataract (P < .001) and posterior segment anomalies (P < .001) were most common in the NOFCD group. Forty-eight (34%) had an associated systemic abnormality, most commonly neurological, musculoskeletal and facial, urological and genital, or cardiac. Neurological abnormalities were most common in the anophthalmic group (P = .003), while urological abnormalities were particularly seen in the OFCD groups (P = .009). Familial cases were identified in both the OFCD and NOFCD groups, with a likely autosomal dominant inheritance pattern in 9 of 10 families.

CONCLUSIONS AND RELEVANCE This series indicated that the OFCD/NOFCD distinction may be useful in guiding evaluation for ocular and systemic associations, as well as the direction and analysis of genetic investigation.


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Microphthalmia, anophthalmia, and coloboma (MAC) are related structural, congenital eye malformations that display a spectrum of severity and can occur in isolation or as part of a syndrome. They account for a significant proportion of childhood visual impairment worldwide. Anophthalmia is the complete absence of the eye. Microphthalmia is a small eye most usefully defined in terms of axial length and corneal diameter. The optic fissure closure defect (OFCD) of coloboma is a segmental ocular defect, affecting some or all of the iris, choroid, retina, and optic nerve. Microphthalmia may also be found in association with congenital cataracts, or when there is disruption of normal anterior segment formation leading to abnormal irides, corneal opacification, and small abnormal lenses.

Reported birth prevalence ranges from 0.6 to 4.2 per 100,000 births for anophthalmia; 2 to 17 per 100,000 births for microphthalmia; and 2 to 14 per 100,000 births for coloboma. In Australia, the incidence of MAC is approximately 6 to 13 per 100,000 births.

The genetic etiology of MAC spectrum disease is not well understood. Clinical and experimental evidence increasingly suggests a heterogenous genetic basis including a local disruption in eye development or as part of a more generalized developmental anomaly. The early development of the eye is controlled by a complex network of diffusible signaling molecules, transcription factors, and downstream targets including cell-cycle regulators, structural proteins, and adhesion factors. The molecular signals in early eye development interact in specific pathways, which may be tissue- and time-specific in their action. This complexity helps explain the overlapping clinical phenotypes and the underlying genetic heterogeneity in these conditions.

In some cases, such as CHARGE (coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies) syndrome or anophthalmia associated with pulmonary hypoplasia, syndrome identification or the presence of a chromosomal anomaly or microdeletion may guide investigations. However, for most patients, no syndrome or chromosomal anomaly is detected. In these cases, molecular diagnosis can be especially challenging because many genes have been identified that are individually responsible for a small number of cases. Currently, the 2 most frequently mutated genes known to cause monogenic MAC are SOX2 and OTX2, accounting for 10% and 3% of cases, respectively, when anophthalmia or severe microphthalmia is present. Mutations in VSX2 (CHX10), PAX6, RAX, FOXE3, BMP4, and GDF6 are less commonly detected. Familial clustering and successful linkage analysis in a small number of families have demonstrated segregation in autosomal recessive or autosomal dominant phenotypes. X-linked recessive or dominant inheritance is associated with some syndromic forms of MAC. Many patients are the first affected individual in their family and this, in combination with the lack of availability of a route to clear-cut genetic diagnosis, hampers informative recurrence risk counseling.

A classification system based on embryological development of the eye may be useful. Morrison et al classified MAC based on the presence or absence of an OFCD. In this study, this classification system was applied to a cohort of patients with MAC to determine the proportions of patients that may fall into these groupings and the associated ocular and systemic features. Cases without a known genetic or syndromic etiology were primarily investigated to determine phenotypic and inheritance patterns. With the advent of broadly targeted next-generation and whole-genome approaches in genetic diagnosis, clear phenotypic characterization will be critical to determine the likelihood that particular molecular variations are disease causing. This clinical knowledge will be useful in directing investigations for possible associated systemic features and for genetic information for affected families.

**Methods**

We performed a retrospective case report study of medical records at the Children’s Hospital, Westmead, Sydney, Australia, from between 1981 and 2012. Ethics approval was prospectively granted by the Children’s Hospital, Westmead, research ethics committee. Because data were collected retrospectively via a database, informed consent was not obtained from patients; all data collected were de-identified from hospital notes. Consecutive cases of microphthalmia, anophthalmia, and coloboma were obtained from the medical records. Inpatient files, outpatient clinic files, and separate files from the Department of Clinical Genetics at the Children’s Hospital, Westmead, were identified via computer database. The search keywords were microphthalmia/microphthalmos, anophthalmia/anophthalamos, nanophthalmia/nanophthalamos, coloboma, and anterior segment dysgenesis (including sclerocornea).

Cases irrelevant to the study, including Axenfield-Rieger spectrum anomalies, Peters anomaly, aniridia, retinopathy of prematurity, and Morning Glory anomaly, were excluded. Cases with a recognized syndrome associated with MAC, such as CHARGE, oculo-auriculo-vertebral spectrum disease, or Joubert syndrome, were excluded.

All cases were reviewed by a senior pediatric ophthalmologist as were first-degree relatives, when possible. The embryological classification proposed by Morrison et al was extended as follows: cases were grouped into microphthalmia with OFCD, microphthalmia without OFCD (NOFCD), microphthalmia unclassified, coloboma isolated in 1 or both eyes (OFCD with normal axial length), and anophthalmia in 1 or both eyes, in keeping with similar studies. Coloboma was defined as a predominantly inferior deficiency of iris, chorioretinal, or optic disc tissue. An iris coloboma was a full-thickness iris defect or anterior stromal deficiency, a chorioretinal coloboma was an area of absent chorioretinal tissue that may or may not extend continuously or discontinuously to the optic disc, and an optic disc coloboma was a focally enlarged optic disc with deficiency of neuroretinal tissue. Microphthalmia was defined as an abnormally small eye or cornea (microcornea) (axial length <16 mm at birth and <19 mm at 12 months of age; and corneal diameter <10 mm at birth). Anophthalmia was defined as no evidence of a globe or ocular tissue in the orbit on
Cases were deemed unclassifiable if the presence or absence of an OFCD was unable to be ascertained; for example, if there was an opaque cornea or indeterminate on ultrasonography.

Cases were further assessed on the basis of the presence or absence of the following features: congenital cataract, anterior or posterior segment morphological abnormality, glaucoma, persistent fetal vasculature (PFV), orbital or nasolacrimal duct abnormality, ocular motility disorder, and systemic abnormalities. Anterior segment abnormality included sclerocornea (defined as a congenital nonprogressive, noninflammatory scleralization of the peripheral and sometimes entire cornea, without underlying iris or angle abnormality or iridocorneal adhesion), abnormal iris (excluding iris coloboma), and disorganized angle. Posterior segment abnormality included chorioretinal or optic disc abnormalities (excluding PFV and chorioretinal and/or optic nerve coloboma); examples included vascular abnormality, chorioretinal atrophy, and hypoplastic and dysplastic optic discs. Visual acuity data were converted into logarithm of the minimal angle of resolution; the visual acuity of the better eye was recorded for each patient.

A detailed systemic clinical evaluation was performed on all patients by a senior pediatrician; further investigation for systemic abnormality was determined by clinical findings.

Significance testing was performed using the $\chi^2$ Fisher exact probability test and analysis of variance across groups. Pedigree analysis was performed to study the pattern of inheritance.

### Results

#### Case Selection

A total of 182 case files were examined, of which 41 were excluded from the study because they did not have MAC spectrum disease. Of those excluded, 19 were anophthalmic secondary to enucleation due to an unrelated cause such as retinoblastoma. A further 22 cases were excluded because they had either a documented congenital infection (3 cases) or a recognized genetic syndrome (19 cases; 7 with CHARGE syndrome, 2 with oculo-auriculo-vertebral spectrum disease, and 1 each of Aicardi Syndrome, Gorlin Syndrome, Jacobsen Syndrome, Nance-Horan Syndrome, Rubenstein-Taybi Syndrome, Waardenburg Syndrome, Norrie Disease, Down Syndrome, Velocardiofacial Syndrome, and Joubert Syndrome), leaving 141 cases in the study. Based on Australian Institute of Health and Welfare data, approximately 235 live births with MAC would be expected in New South Wales during the study period, indicating a 60% capture rate of all New South Wales cases in this study.

#### Descriptive Data

Most cases were detected in the first 18 months of life, with the median age at presentation being 11 months (Table 1). The mean better-eye visual acuity corresponded to Snellen 6/45 (range, 6/4.5 to no light perception). The sex distribution was broadly equal, with 73 males and 68 females. There were 63 bilateral and 78 unilateral cases. There were 61 cases (43%) with microphthalmic NOFCD and 66 cases with OFCD, in whom 34 (24%) had an eye size meeting the definition for microphthalmia and 32 (23%) where the eye size did not meet the microphthalmia definition. In 5 cases, the presence or absence of an OFCD could not be determined. Nine patients had anophthalmia; this was bilateral in 7 cases. In the 2 patients with unilateral...
eral anophthalmia, the other eye had an OFCD in one patient and there was an NOFCD in the other eye in the other patient. Eighty-four patients (60%) had an associated ocular abnormality in their involved eye(s); 48 (34%) had an associated systemic abnormality. Thirty-eight individuals received surgical intervention, the most common procedure being a lensectomy.

MAC Subgroup Analysis
There were no differences between MAC subgroups in terms of bilateralality; however, on subgroup analysis of the NOFCD group, microphthalmic eyes with PFV had fewer bilaterally affected cases ($P < .007$). Table 2 demonstrates the distribution of associated ocular abnormalities within the subgroups. Associated ocular abnormalities were most common in the NOFCD (53 of 61) and microphthalmic OFCD (20 of 34) groups, and they were less common in the nonmicrophthalmic OFCD group (7 of 32) ($P < .001$). The most common abnormality was congenital cataract (45 of 141), which was the most frequently associated ocular anomaly in the NOFCD group (37 of 61). However, it was also present in both in the microphthalmic (7 of 34) and nonmicrophthalmic (1 of 32) OFCD groups, indicating some overlap in phenotypic features between the groups. Other associated ocular features in the NOFCD group were posterior segment anomalies (27 of 61), including persistent fetal vasculature, anterior segment abnormalities, such as opacifications of the cornea in 11 of 61 patients. Ocular motility disorders were least prevalent in the nonmicrophthalmic coloboma (OFCD) group ($P = .04$).

An associated systemic abnormality was identified in 34% of cases. The frequency and type of systemic abnormality did not vary between unilateral and bilateral cases. The distribution of systemic abnormalities found in our cohort is shown in Table 3, and several patients had more than 1 associated systemic feature. The most common abnormalities were neurological, musculoskeletal and facial, and urological and genital. Neurological abnormality was most common in the anophthalmic subgroup (5 of 9) and least in the nonmicrophthalmic OFCD group (1 of 32) ($P = .003$). Urological and genital abnormality was most common in the microphthalmic (5 of 34) and nonmicrophthalmic (7 of 32) OFCD groups and least common in the anophthalmic group (0 of 9) ($P = .009$). Cardiac abnormality was not detected in the NOFCD group (0 of 61) and was present in all other groups in small numbers ($P = .04$).

Sibling Recurrence
Microphthalmia, anophthalmia, and coloboma disease was recorded in 23 individuals from 10 families in our cohort. Expression within families remained consistently either NOFCD or OFCD; however, within families, some individuals were microphthalmic and others had normal ocular size. This indicates variable phenotypic expression of the genetic defect. Six of the families had NOFCD, with cataracts and microphthalmia running in an autosomal dominant inheritance pattern. Offspring in 1 of these families had associated features of iridocorneal adhesions and sclerocornea. Four of the familial cases had OFCD and these followed an autosomal dominant inheritance pattern in 3 cases. In the other OFCD family, nonconsanguineous unaffected parents had 2 affected children, 1 female and 1 male. This may be owing to autosomal recessive inheritance or to germline mosaicism with or without somatic mosaicism in 1 of the phenotypically unaffected parents.

Discussion
There have been a variety of classification systems for MAC spectrum disorders but, to our knowledge, few have attempted to classify the phenotypic features based on embryology and possible genetic etiology. The early embryology of the eye includes several important events (optic vesicle formation, optic cup formation, and optic fissure closure), which provide points for consideration of the responsible molecular signals, pathways, and genetic coordinators. From a clinical perspective, the microphthalmic NOFCD group may represent either a very severe phenotype suggesting disruption at the optic vesicle or optic cup stage or, if mild, then interruption to differentiation and maturation. The presence of OFCD implies disruption to events around the time of optic fissure closure. There has been some epidemiological evidence for subclassifying MAC spectrum disorders according to the presence or absence of a coloboma.

There have been recent advances in our understanding of the genetic etiology of microphthalmia and anophthalmia spectrum disorders largely through family studies and clinical molecular testing for some candidate genes is now available. Because microphthalmia and anophthalmia spectrum has a heterogenous genetic etiology with a variety of phenotypic expressions, specific candidate genes for

### Table 2. Relative Prevalence of Associated Ocular Abnormalities Within MAC Subgroups

<table>
<thead>
<tr>
<th>Ocular Abnormality</th>
<th>NOFCD (n = 61)</th>
<th>OFCD (n = 34)</th>
<th>Unclassified (n = 5)</th>
<th>OFCD (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior segment</td>
<td>11 (18)</td>
<td>7 (21)</td>
<td>1 (20)</td>
<td>2 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Cataract</td>
<td>37 (61)</td>
<td>7 (21)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Posterior segment</td>
<td>27 (44)*</td>
<td>6 (18)</td>
<td>1 (20)</td>
<td>1 (3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>10 (16)</td>
<td>1 (3)</td>
<td>1 (20)</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Orbital/nasolacrimal duct</td>
<td>3 (5)</td>
<td>2 (6)</td>
<td>1 (20)</td>
<td>1 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ocular motility</td>
<td>23 (38)</td>
<td>10 (30)</td>
<td>2 (40)</td>
<td>3 (9)</td>
<td>.04</td>
</tr>
<tr>
<td>Any ocular abnormality</td>
<td>53 (87)</td>
<td>20 (59)</td>
<td>4 (80)</td>
<td>7 (22)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: MAC, microphthalmia, anophthalmia, and coloboma; NOFCD, nonoptic fissure closure defect; NS, not significant; OFCD, optic fissure closure defect.

* Including 16 cases with persistent fetal vasculature.
Table 3. Relative Prevalence of Associated Systemic Abnormalities Within MAC Subgroups

<table>
<thead>
<tr>
<th>Systemic Abnormality</th>
<th>No. (%)</th>
<th>Microphthalmic</th>
<th>NOFCD (n = 61)</th>
<th>OFCD (n = 34)</th>
<th>Unclassified (n = 5)</th>
<th>Nonmicrophthalmic</th>
<th>OFCD (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic optic nerves and tracts; septo optic dysplasia; occipital encephalocoele; frontal encephalocoele; bilateral sensorineural hearing loss and absent septum pellucidum</td>
<td>Sensoryneural hearing loss and atrophic optic chiasm; sensoryneural hearing loss; bilateral sensorineural hearing impairment; congenital right cerebral hypoplasia, bifid pitiary, and small corpus callosum; severe developmental delay; hypotonia; hydrocephalus; midline hypothyamus and optic chiasm anomaly</td>
<td>1: Sensoryneural hearing loss; hydrocephalus; basal encephalocoele, corpus callosum agenesis; absent septum pellucidum with dilated lateral ventricles, hydrocephalus, and atrophic corpus callosum; occuit spinai bifida; involuntary arm movements; epilepsy</td>
<td></td>
<td></td>
<td>1: Absent cerebellar vermis and expressive dysphasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (11):</td>
<td>5 (8):</td>
<td>8 (24):</td>
<td>0 (0)</td>
<td></td>
<td>2 (6):</td>
<td></td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>Absent right ear, cleft lip, and palate</td>
<td>Short palpebral fissures, microcephalus, wide nasal bridge, small posteriorly rotated ears and syndactyly of toes 2–3, limb overgrowth; polydactyly; abnormal dentition, right facial microsomia, malar hypoplasia, small jaw, redundant upper eyelids, downsloping palpebral fissures, fused C2–3, scoliosis, and nasal deformity; 11 ribs bilaterally, sacral hemivertebrae, tracheo-esophageal fistula, low rotated ears, flat facies, fused eyelids</td>
<td>Facial dysmorphology, down slating palpebral fissures, wide nasal bridge, short nose, micrognathia, rotated ears, and nuchal thickening; bilateral 5th finger clinodactyly and override toes 2–3; subaortic stenosis, bilateral limb abnormalities, bilatrol malformations of heart</td>
<td>0 (0)</td>
<td>2 (6): Fused C2–3, postaxial polydyactyly both upper limbs and left lower limb; cleft palate, hyperflexible thumb joints, Klippel–Feil anomaly C2–C4, high nasal bridge, proptorberent lower lip, pectus excavatum, malor hypoplasia and long feet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>1 (11):</td>
<td>5 (15):</td>
<td>0 (0)</td>
<td>1 (20):</td>
<td></td>
<td>1 (6):</td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>Hemitrunrunc arteriosum, ventricular septal defect, and pulmonary hypertension</td>
<td>Ventricular septal defect; patent ductus arteriosus; pulmonary atresia, ventricular septal defect, atrial septal defect; ventricular septal defect, atrial septal defect, patent ductus arteriosus; atrial–ventricular septal defect</td>
<td>2: Ventricular septal defect</td>
<td>Tetralogy of Fallot</td>
<td>2 (6): Subaortic stenosis; ventricular septal defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urological and genital</td>
<td>0 (0)</td>
<td>1 (2): Hydrocele</td>
<td>5 (15): Anterior anus and hypoplastic labia majora; vesicoureteric reflux; renal pelvic dilatation; microopens and absent scrotum; neurogenic bladder and renal reflex</td>
<td>1 (20): Congenital left testicular torsion</td>
<td>7 (22): Undescended testes; severe vesicoureteric reflux; medullary stone kidneys; single kidney; cryptorchidism; dysplastic kidney; bladder abnormalities, dysplastic kidneys</td>
<td>1: Hydrocele</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integumentary</td>
<td>1 (11):</td>
<td>2 (3): Hypopigmented skin patches; hirsutism</td>
<td>1 (3): Café au lait spot on left shoulder</td>
<td>0 (0)</td>
<td>1 (3): Dry skin, sparse hair</td>
<td>4 (12): Uginual hernia; 2-vessel umbilicus with hernia; plagaicolealy; hepatitisologemoly</td>
<td>0 (0)</td>
<td>.56</td>
</tr>
<tr>
<td>Other systemic abnormality</td>
<td>0 (0)</td>
<td>3 (5): Reduced growth hormone; congenital cystic adenoid malformation of lung type II and duodenal atresia; obstructive sleep apnea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (12): Uginual hernia; 2-vessel umbilicus with hernia; plagiochely; hepatitisologemoly</td>
<td>0 (0)</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6 (67)</td>
<td>15 (25)</td>
<td>13 (38)</td>
<td>2 (40)</td>
<td>12 (38)</td>
<td></td>
<td></td>
<td>.13</td>
</tr>
</tbody>
</table>

Abbreviations: MAC, microphthalmia, anophthalmia, and coloboma; NOFCD, nonoptic fissure closure defect; OFCD, optic fissure closure defect.

Microphthalmia and anophthalmia can only be isolated in a minority of cases. In the near future, whole-exome sequencing, with interpretation guided by an understanding of the overlapping roles of developmental genes in OFCD and NOFCD, will lead to increased yield in diagnostic testing in these conditions (Figure). This is likely to significantly enhance our understanding of the genetic etiology of these disorders.

The Australian prevalence of MAC is comparable with other countries: 1 to 17 per 100,000 births for microphthalmia, with variability largely based on different inclusion/exclusion criteria. The sex distribution of our cases was approximately equal, in keeping with other studies. It is possible that these were the more severe cases in this spectrum of disorders or they may have had concomitant problems leading to a referral for management.
Epidemiological studies have suggested that cataract is often found in association with microphthalmia. Our finding that cataract was the most frequently associated eye abnormality in the NOFCD cohort (Table 2) and can be found in relatives of patients with NOFCD is consistent with these reports. There have been previous instances of pedigrees with this pairing of eye abnormalities. Anterior segment anomalies were more common in the microphthalmic OFCD group than the non-microphthalmic OFCD group. This may reflect an increased incidence of corneal abnormality and anterior segment disorganization in microphthalmic eyes. Glaucoma (an important comorbidity) affected a small number of patients in all groups. Ocular motility abnormalities were present in all microphthalmic groups, consistent with a higher incidence of poor vision in microphthalmic eyes and subsequent sensory tropia.

Similar to previous studies, a large proportion of our cases (34%) had an associated systemic abnormality, most commonly neurological, muscularkeletal and facial, or urological and genital. Neurological abnormality was relatively more common in the anophthalmic OFCD group followed by the microphthalmic OFCD and NOFCD groups (Table 3). This is in keeping with previous studies where neurological abnormality, especially midline anomalies, have been found, particularly when the eyes are more severely affected. Optic fissure closure defect cases, both microphthalmic and non-microphthalmic, showed an increased predisposition to urological abnormalities compared with NOFCD cases. By excluding cases with known syndromic etiology to provide clues to possible nonsyndromic systemic associations, this cohort may reflect a reduced incidence of systemic abnormalities associated with MAC.

In this series, most pedigrees had an autosomal dominant inheritance pattern. However, most cases did not have a known family history. Sibling recurrence is a significant risk and must be explained to affected families. In this series, there were familial cases in both the NOFCD (6 families) and OFCD (4 families) groups. There was marked variability within some families. For example, there was 1 family where a father had coloboma with normal size eyes, while his child had coloboma and microphthalmia. Three NOFCD families had individuals with microphthalmia and cataracts, whose relatives (typically earlier generations) had pediatric cataract with normal globe size.

Persistent fetal vasculature, traditionally considered a separate clinical entity, has been included as a subset of NOFCD within this cohort. With increasing identification of causative genes, there may be an etiological overlap between PFV and the noncolobomatous cases of microphthalmia. When compared with non-PFV cases in the NOFCD group, those with PFV had similar frequencies of systemic and ocular abnormalities; however, there was a higher prevalence of unilateral cases.

Five of the cases classified as microphthalmic on the basis of small corneal diameters were subsequently shown to have normal axial lengths when this was measured in later childhood. Each of these cases had associated bilateral congenital cataracts and had developed glaucoma or had an affected family member with congenital cataract and microphthalmia. These cases represent a distinct clinical subset that requires recognition by the pediatric ophthalmologist and geneticist. Patients with the phenotype of cataract and microcornea, with or without reduction in axial length, may have mutations in cataract-related genes such as GJA8, GJA3, CRYBA4, and CRYGC.

This study provided useful clues for clinicians and geneticists involved in the management of these patients. First, the phenotypic expression of MAC spectrum abnormalities is variable (even within families) and a significant proportion of the patient population has associated eye and systemic abnormalities and careful examination must be made for these. Some of these, such as NOFCD with cataract and OFCD with urological abnormalities, cluster together and this serves as an aid to the clinician in recognizing these associations. While the inheritance pattern is complex and incompletely understood, it is clear that cases of bilateral MAC abnormalities and those NOFCD cases with cataract may be particularly associated with a familial pattern of inheritance. Expression of MAC spectrum disorders is not uniform, so the clinical delineation of phenotypic features is important to aid interpretation of exome and whole-genome data in these patients as this becomes increasingly available. This will lead to improved prospects for genetic diagnosis and information for these patients and families.
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Author Contributions: Dr Jamieson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Skalicky, White, Martin, Donaldson, J. E. H. Smith, Flaherty.

Analysis and interpretation of data: Skalicky, White, J. Smith, Jones, Jamieson.

Drafting of the manuscript: Skalicky, White, Grigg, Jamieson.

Critical revision of the manuscript for important intellectual content: Skalicky, White, Martin, J. Smith, Jones, Donaldson, J. E. H. Smith, Flaherty, Jamieson.

Statistical analysis: Skalicky, Grigg.

Obtained funding: Grigg.

Administrative, technical, or material support: Skalicky, Grigg, Donaldson.

Study supervision: Grigg, Martin, Jones, Donaldson, J. E. H. Smith, Jamieson.

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REFERENCES


