Review of literature
The eye is made of three parts.

- A light focusing bit at the front (cornea and lens).
- A light sensitive film at the back of the eye (retina).
- A large collection of communication wires to the brain (optic nerve).

A curved window called the cornea first focuses the light. The light then passes through a hole called the pupil. A circle of muscle called the iris surrounds the pupil. The iris is the coloured part of the eye. The light is then focused onto the back of the eye by a lens. Tiny light sensitive patches (photoreceptors) cover the back of the eye. These photoreceptors collect information about the visual world. The covering of photoreceptors at the back of the eye forms a thin film known as the retina. Each photoreceptor sends its signals down very fine wires to the brain. The wires joining each eye to the brain are called the optic nerves. [Weiss et al 1989] The information then travels to many different special 'vision' parts of the brain. All parts of the brain and eye need to be present and working for us to see normally. [Annual Report 2003]

Microphthalmia
When a baby is growing in the womb sometimes not all the parts of the baby grow fully. If an eye does not grow to its full size and is smaller (micro) than it should be this is known as Microphthalmia. If the eye does not grow at all then this is known as Anophthalmia. [Morrison et al 2002]

Microphthalmia is an eye abnormality that arises before birth. In this condition, one or both eyeballs are abnormally small. In some affected individuals, the eyeball may appear to be completely missing; however, even in these cases some remaining eye tissue is generally present. Such severe microphthalmia should be distinguished from another condition called anophthalmia, in which no eyeball forms at all. However, the terms anophthalmia and severe microphthalmia are often used interchangeably. Microphthalmia may or may not result in significant vision loss. [Campbell et al 2002]
Microphthalmia

- Clouding of the lens of the eye (cataract)
- Micro cornea, (cornea) is small and abnormally curved
- A narrowed opening of the eye (narrowed palpebral fissure)

People with microphthalmia may also have a condition called coloboma. Colobomas are missing pieces of tissue in structures that form the eye. They may appear as notches or gaps in the coloured part of the eye called the iris; the retina, which is the specialized light-sensitive tissue that lines the back of the eye; the blood vessel layer under the retina called the choroid; or in the optic nerves, which carry information from the eyes to the brain.[Shah et al 2011]

Colobomas may be present in one or both eyes and, depending on their size and location, can affect a person's vision. [Brooks et al 2005]

People with microphthalmia may also have other eye abnormalities, including clouding of the lens of the eye (cataract) and a narrowed opening of the eye (narrowed palpebral fissure) [Campbell H et al 2002]. Additionally, affected individuals may have an abnormality called microcornea, in which the clear front covering of the eye (cornea) is small and abnormally curved.[Shaw et al 2005]

Between one-third and one-half of affected individuals have microphthalmia as part of a syndrome that affects other organs and tissues in the body.[Kallen et al 1996] These forms of the condition are described as syndrome. When microphthalmia occurs by itself, it is described as nonsyndromic or isolate.[Forrester et al 2006]

The mean maximum axial lengths in the neonatal and adult human eye are approximately 17 and 23.8 mm respectively. Most of the post-natal growth of the eye occurs within the first three years with posterior segment expansion accounting for over 90% of post-natal growth. The International Clearinghouse for Birth Defects Monitoring Systems defines anophthalmia and microphthalmia as "anophthalmos/microphthalmos: apparently absent or small eyes."
Some normal adnexal elements and eyelids are usually present. In microphthalmia, the corneal diameter is less than 10 mm, and the antero-posterior diameter of the globe is less than 20 mm” [Annual Report 2003. Rome].

Anophthalmia refers to complete absence of the globe in the presence of ocular adnexa (eyelids, conjunctiva, and lacrimal apparatus).

Microphthalmia refers to a globe with a total axial length (TAL) that is at least two standard deviations below the mean for age (see Table 1). For an adult eye, the lower 2.5% confidence limit for the TAL is about 21.0 mm. In a child in whom postnatal ocular growth continues into adolescence, the lower 2.5% confidence limit must be derived from a normative plot of TAL versus age [Mann et al 1953]

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean Length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Axial Length</td>
</tr>
<tr>
<td>Neonate</td>
<td>17 mm</td>
</tr>
<tr>
<td>Adult</td>
<td>23.8 mm</td>
</tr>
</tbody>
</table>

1. Total axial length (TAL) is the axial distance (in mm) from the corneal apex to the back of the globe.

2. Anterior segment length (ASL) is the axial distance (in mm) from the cornea to the back of the lens.

3. Posterior segment length (PSL) is the axial distance (in mm) from the back of the lens to the back of the globe.

In microphthalmic eyes, measurements of ASL and PSL indicate that ASL is within or below the normal range, whereas PSL is uniformly at least two standard deviations below the mean for age.

Most postnatal growth of the eye occurs in the first three years of life, particularly during the first year. Growth of the posterior segment accounts for 60% of the prenatal and more than 90% of the postnatal increase in TAL. Although TAL is reduced at birth, the microphthalmic eye...
can grow by a variable amount in the postnatal period depending upon the severity of the underlying malformation. [Morrison et al 2002]

**Epidemiology**

The birth prevalence of anophthalmia and microphthalmia has been generally estimated to be 3 and 14 per 100,000 population respectively, although other evidence puts the combined birth prevalence of these malformations at up to 30 per 100,000 population [Morrison et al 2002]. Epidemiological data suggests risk factors for these conditions are maternal age over 40, multiple births [Kallen et al 1996], infants of low birth weight and low gestational age. There is no predilection with regards to race or gender. Both anophthalmia and microphthalmia are more commonly bilateral; the exception appears to be isolated microphthalmia, which is usually unilateral. Microphthalmia is reported in 3.2 – 11.2% of blind children [Forrester et al 2006].

**Clinical description**

Anophthalmia refers to the absence of ocular tissue in the orbit. In the absence of clinically apparent ocular tissue, histological sectioning has shown residual neuroectoderm in some cases and hence terms such as ‘true anophthalmia’, ‘clinical anophthalmia’ and ‘extreme microphthalmia’ may in fact refer to what is in reality a phenotypic range between anophthalmia and microphthalmia. Clinically it seems reasonable to use the term microphthalmia for an eye with axial length two standard deviations below that of the population age-adjusted mean; this typically correlates to an axial length below 21 mm in adult eyes. Simple microphthalmia refers to a structurally normal, small eye, and has been used interchangeably with ‘nanophthalmia’ (though the latter is particularly used when referring to a small eye with microcornea, axial length <18 mm, and = 8D hypermetropia). [Campbell et al 2002]

The increased thickness of the sclera in these eyes and the subsequent changes in blood flow are believed to be responsible for the increased incidence of uveal effusions and choroidal detachments seen. Microphthalmia may also be associated with other ocular disorders, in which case it is termed complex microphthalmia. These ocular disorders may affect the anterior segment (for example, sclerocornea and Peter’s anomaly) and/or the posterior segment (for example, persistent hyperplastic primary vitreous and retinal dysplasias). Both anophthalmia and microphthalmia can occur in isolation or be syndromic, as in about one-third of cases (see additional files 1 and 2 for a review of syndromes associated with anophthalmia and microphthalmia respectively). Learning disabilities are seen in approximately one-fifth of cases. [Morrison et al 2002]. Complex microphthalmia, in particular, exhibits wide phenotypic variability.
Classification of microphthalmia
Classification of microphthalmia is according to the anatomic appearance of the globe and severity of axial length reduction.

Severe microphthalmia
Severe microphthalmia refers to a globe that is severely reduced in size, with a corneal diameter less than 4 mm and a TAL less than 10 mm at birth or less than 12 mm after age one year. Although the globe is inconspicuous on clinical examination, CT or MRI reveals remnants of ocular tissue, an optic nerve, and extraocular muscles. Without orbital imaging studies, severe microphthalmia can be mistaken for anophthalmia; thus, the term "clinical anophthalmia" is often inappropriately used for severe microphthalmia.

Simple microphthalmia refers to an eye that is anatomically intact except for its short TAL. Decreases in TAL are usually mild in simple microphthalmia. Simple microphthalmia is suspected in the presence of high hyperopia (≥8 diopters) or microcornea, which is present in about 15% of affected individuals. A subset of individuals can have visual loss resulting from posterior segment abnormalities including papillomacular folds, macular hypoplasia, cystoid macular edema, and uveal effusion. Nanophthalmia is a subtype of simple microphthalmia characterized by microcornea, TAL less than 18 mm, and high hyperopic (≥8 dioptres). Angle-closure glaucoma is common.

Complex microphthalmia
Refers to an eye with anterior segment dysgenesis and/or posterior segment dysgenesis. Decreases in TAL can be mild, moderate, or severe. Anterior segment dysgenesis includes a spectrum of developmental abnormalities of the cornea, iris, iridocorneal angle, and ciliary body: Axenfeld-Rieger anomaly. Axenfeld anomaly (a prominent and centrally displaced Schwalbe's line [posterior embryotoxon] with bands of iris tissue bridging the iridocorneal angle) combined with a spectrum of central iris defects including diffuse iris hypoplasia with a normally positioned or eccentric pupil (corectopia) or segmental iris aplasia resulting in multiple pupils (polycoria)

Note: The term "anomaly" designates the ocular findings alone, whereas the term "syndrome" includes systemic findings such as dental anomalies, maxillary hypoplasia, ocular hypertelorism, cutis navel, and heart defects. [Fitzpatrick et al 2005]
Causes of anophthalmia and microphthalmia

Microphthalmia may be caused by changes in many genes involved in the early development of the eye, most of which have not been identified. The condition may also result from a chromosomal abnormality affecting one or more genes. Most genetic changes associated with isolated microphthalmia have been identified only in very small numbers of affected individuals. [Morrison et al 2002]

Researchers also believe that environmental factors, such as exposure to X-rays, chemicals, drugs, pesticides, toxins, radiation, or viruses, increase the risk of anophthalmia and microphthalmia [Forrester et al 2006].

Aetiology

The precise pathogenesis of anophthalmia and microphthalmia remains unknown. Mann suggested anophthalmia has its genesis early in gestation as a result of failure of development of the anterior neural tube (secondary anophthalmia) or optic pit(s) to enlarge and form optic vesicle(s) (primary anophthalmia). A third category, consecutive or degenerative anophthalmia was applied to cases where optic vesicles have degenerated and disappeared subsequent to formation. Observations of optic nerves, chiasm, and/or tracts with anophthalmia may indicate the regression of a partially developed eye rather than aplasia of the optic vesicle(s), a view supported by observations in an apparently anophthalmic orbit of extraocular muscle insertion into a fibrous mass, possibly representing an aborted eye [Weiss et al 1989]. Following observations that the posterior segment of microphthalmic eyes are more affected than the anterior, [Guthoff et al 2004] suggest that post-natal ocular growth is crucial and speculated that decreased size of the optic cup, altered proteoglycans in the vitreous, low intraocular pressure and abnormal growth factor production may all or in part have a bearing on the pathogenesis of simple microphthalmia; whilst inadequate production of secondary vitreous may result in complex microphthalmia. Some cases of microphthalmia may be associated with a cyst; these are believed to result from failure of the optic fissure to close [Fantes et al 2003].

Epidemiological studies have predicted both heritable and environmental factors in causing anophthalmia and microphthalmia. This review focuses on heritable causes as the evidence for environmental causes is both more circumstantial and accounts for a smaller proportion of cases.

Mutations in three genes with retinal expression are associated with anophthalmia/microphthalmia, possibly through failure of retinal differentiation. Heterozygous loss-of-function mutations of OTX2(on chromosome 14q22, autosomal dominant inheritance)
have been shown to be associated with a wide range of ocular disorders from anophthalmia and microphthalmia to retinal defects. CNS malformations and mental retardation are common in patients with OTX2 mutations [Ragge et al 2005]. RAX, located on chromosome 18q21.32, is linked to about 2% of inherited anophthalmia/microphthalmia[Williamson et al 2005]. Similarly, CHX10 mutations (chromosome 14q24.3) account for about 2% of isolated microphthalmia mutations in both genes characteristically presenting with recessively inherited [Billingsley et al 2006].

**Syndromes associated with microphthalmia.**

**Table 1**

Chromosomal abnormalities associated with anophthalmia/microphthalmia [Morrison et al 2002].

<table>
<thead>
<tr>
<th>Chromosomal Abnormality</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplication 3q syndrome (3q21-ter dup)</td>
<td>Learning difficulties, growth deficiency, hypertrichosis, craniosynostosis, cardiac defects, chest deformities, genital abnormalities, umbilical hernia</td>
</tr>
<tr>
<td>4p- (Wolf-Hirschhorn syndrome)</td>
<td>Growth deficiency, microcephaly, ocular hypertelorism, cranial asymmetry, learning difficulties, epilepsy, cleft lip/palate, anterior segment dysgenesis</td>
</tr>
<tr>
<td>Duplication 4p syndrome</td>
<td>Learning difficulties, epilepsy, growth deficiency, obesity, microcephaly, characteristic faces, genital abnormalities, kyphoscoliosis</td>
</tr>
<tr>
<td>Deletion 7p15.1-p21.1</td>
<td>Cryptophthalmos, cleft lip/palate, choanal atresia</td>
</tr>
<tr>
<td>Trisomy 9 mosaic syndrome</td>
<td>Joint contractures, congenital heart defects, prenatal growth deficiency, learning difficulties, micrognathia, kyphoscoliosis</td>
</tr>
<tr>
<td>Duplication 10q syndrome</td>
<td>Ptosis, short palpebral fissures, camptodactyly, learning difficulties, prenatal growth deficiency, microcephaly, heart and kidney malformations</td>
</tr>
<tr>
<td>13q-, 13 ring</td>
<td>Microcephaly, learning difficulties, bilateral retinoblastoma, cardiac defects, hypospadias, cryptorchidism</td>
</tr>
</tbody>
</table>
Trisomy 13 (Patau syndrome)  Holoprosencephaly, moderate microcephaly, coloboma, retinal dysplasia, cyclopia, cleft lip/palate, cardiac defects, genital abnormalities, 86% die within one year.

Deletion 14q22.1-q23.2  Pituitary hypoplasia.

18q-  Midface hypoplasia, small stature, learning difficulties, hypotonia, nystagmus, conductive deafness, microcephaly, midface hypoplasia, genital abnormalities

Trisomy 18 (Edwards syndrome)  Polyhydramnios, single umbilical artery, small placenta, low foetal activity, learning difficulties, hypertonicity, hypoplasia of skeletal muscle, subcutaneous, adipose tissue, prominent occiput, low-set malformed auricles, micrognathia, cardiac defects

Triploidy syndrome  Large placenta with hydatidiform changes, growth deficiency, syndactyly, congenital heart defects, brain anomalies/holoprosencephaly

Table 2


<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus (Inheritance)</th>
<th>Major (and selected less common) Human Ocular Phenotype(s)</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOX2</td>
<td>3q26.3-q27 (AD)</td>
<td>Anophthalmia/microphthalmia</td>
<td>184429</td>
</tr>
<tr>
<td>PAX6</td>
<td>11p13 (AD)</td>
<td>Aniridia, (Peters anomaly, autosomal dominant keratopathy, foveal hypoplasia, optic nerve malformations, anophthalmia)</td>
<td>607108</td>
</tr>
<tr>
<td>OTX2</td>
<td>14q22 (AD)</td>
<td>Anophthalmia/microphthalmia, (retinal dysplasia, optic nerve malformations)</td>
<td>600037</td>
</tr>
<tr>
<td>RAX</td>
<td>18q21.3 (AR)</td>
<td>Anophthalmia/microphthalmia</td>
<td>601881</td>
</tr>
</tbody>
</table>
Genetic counselling
Genetic counselling is challenging both from the perspective of the extensive range of genes responsible for anophthalmia/microphthalmia and the wide variation in phenotypic expression. Only SOX2 has thus far been identified as a major anophthalmia/microphthalmia gene, with mutations primarily arising de novo. The picture is further complicated by observations of phenotypically normal parents carrying loss of function SOX2 or OTX2 mutations [Bronshtein et al 1991]. Mosaicism and/or variable penetrance render prediction of recurrence risk difficult in these monogenic anophthalmia/microphthalmia cases. In general, if the mode of inheritance can be identified, then appropriate counselling is indicated. The empiric risk to siblings without a clear aetiology or family history is 10–15%, assuming inheritance accounts for half of cases with the other half occurring sporadically. Chromosomal abnormalities associated with anophthalmia/microphthalmia tend to be associated with distinct co-morbidities and give rise to specific syndromes. If a patient has a numerical chromosomal abnormality, the parents can be expected to be entirely normal whilst siblings are at a slightly increased risk of having a similar chromosomal abnormality, with similar or dissimilar phenotype. If a patient has a structurally unbalanced chromosomal constitution, the parents may have balanced chromosomal rearrangements and other siblings will be at a higher risk, though this will depend upon the specific rearrangement. If neither parent has any rearrangement, the risk to siblings is virtually negligible [Mann 1953].

Antenatal diagnosis

Chromosome analysis
Cytogenetic studies are possible upon amniotic fluid foetal cells (usually withdrawn after 14 weeks of gestation) or on chorionic villus sampling specimens (at about 10 to 12 weeks). The power of these techniques in facilitating the pre-natal diagnosis of

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Phenotype Description</th>
<th>OMIM Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHX10</td>
<td>14q24.3 (AR)</td>
<td>Microphthalmia</td>
<td>142993</td>
</tr>
<tr>
<td>FOXE3</td>
<td>1p32</td>
<td>Anterior segment dysgenesis, congenital primary aphakia</td>
<td>601094</td>
</tr>
<tr>
<td>CRYBA4</td>
<td>22q11.2-q13.1 (AD)</td>
<td>Autosomal dominant cataract, (microphthalmia)</td>
<td>123631</td>
</tr>
</tbody>
</table>
anophthalmia/microphthalmia was elegantly demonstrated a foetus with severe intrauterine growth retardation and bilateral anophthalmia on a 24-week ultrasound scan, they demonstrated a 46, XX, del(3)(q26.3q28) interstitial deletion of the long arm of chromosome 3 on 650 band karyotype. FISH analysis confirmed the interstitial deletion of 3q27 encompassing the SOX2 locus. [Chen et al 2003]

**Ultrasonography**

It is possible to detect anophthalmia/microphthalmia by early second trimester [Mashiach et at 2004], though more recent reports place the limit at about 12 weeks with trans-vaginal ultrasound [Blazer et al 2006]. Foetal eyes are best scanned in the coronal, axial and corono-axial planes and appear as symmetrical structures on either side of the nose. Lenses appear as smooth circular lines with hypoechogenic content on axial and coronal views. Eye size can be measured upon visualising the maximum coronal or axial planes of the orbit, and compared against established eye growth charts [Clauser et al 2004].

MRI where available can be used to supplement ultrasonography.

**Management**

**Conservative**

Detectable retinal function may be present in microphthalmia cases, particularly those associated with SOX2 mutations. It is important to refract these eyes and treat any underlying amblyopia. In unilateral cases, the 'good' eye must be protected and any visual deficit managed appropriately.

**Surgical**

Surgical management can form the mainstay of anophthalmia/microphthalmia treatment. The globe triples in volume between birth and adolescence. The growth of the bony orbit reflects growth of the globe. Both congenital anophthalmia and microphthalmia result in a small volume orbit compared to age-matched controls [McLean 2004], potentially leading to the appearance of hemifacial asymmetry. There is also evidence that enucleation (removal of the globe) produces a reduction in orbital volume in both children and adults. Reconstructive strategies rely upon the simultaneous management of both soft tissue hypoplasia and asymmetric bone growth [Brooks et al 2005].

Treatment is usually started early to maximise the overall development of these children. Mild/moderate microphthalmia is generally managed conservatively with insertion of a
conformer (like a prosthetic eye but not painted), periodically increasing in size to allow for growth of the orbit. Treatment for severe microphthalmia and anophthalmia are usually started within weeks of life using conformers to enlarge the palpebral fissure, conjunctival cul-de-sac and orbit. Endo-orbital volume replacement using implants of progressively increasing size can be used to stimulate expansion of the developing bony orbit, usually after six months of age. Volume replacement using implants and expanders can also be supplemented by the use of dermis-fat grafts. Static orbital implants may need to be changed between three and five times before puberty and are associated with problems of wound dehiscence, extrusion or inadequate stimulation of bony growth. Expandable orbital implants were introduced as an efficacious means of stimulating bony growth and socket enlargement. Inflatable expanders are limited by difficulty maintaining orbital fixation for sustained expansion and controlling the direction of expansion, whilst self-expanding hydrogel spheres lose expansion force once fully hydrated. Orbital osteotomies are indicated in more severe cases. Ocular prostheses are used when the orbit has developed adequately, and are changed regularly with further orbital expansion. Conjunctival sac and lid reconstruction may be beneficial to the overall cosmetic effect. Microphthalmia with cyst is often treated around the age of five permitting the ophthalmic surgeon to take advantage of the orbital expansion properties of the cyst until the orbit is about 90% of the adult volume, whilst allowing removal for cosmetic reasons at about the time the child starts school. Surgical excision with preceding decompression is commonly performed, the cyst may also be aspirated but the recurrence rate is higher [Brooks et al 2005].

**Prognosis**

The potential for visual development depends upon the degree of retinal development and other ocular characteristics in microphthalmic patients. Therapy aims to maximise existing vision and enhance cosmetic appearances rather than improve sight.

**Treatment of anophthalmia and microphthalmia**

There is no treatment for severe anophthalmia or microphthalmia that will create a new eye or restore vision. However, some less severe forms of microphthalmia may benefit from medical or surgical treatments. In almost all cases improvements to a child's appearance are possible. Children can be fitted for a prosthetic (artificial) eye for cosmetic purposes and to promote socket growth. [Ragge et al 2005]

A newborn with anophthalmia or microphthalmia will need to visit several eye care professionals, including those who specialize in pediatrics, vitreoretinal disease, orbital and oculoplastic surgery, ophthalmic genetics, and prosthetic devices for the eye. Each specialist
can provide information and possible treatments resulting in the best care for the child and family. [Ferda et al 2002]

The specialist in prosthetic diseases for the eye will make conformers, plastic structures that help support the face and encourage the eye socket to grow. As the face develops, new conformers will need to be made. A child with anophthalmia may also need to use expanders in addition to conformers to further enlarge the eye socket. Once the face is fully developed, prosthetic eyes can be made and placed. Prosthetic eyes will not restore vision.

Tinted glasses can also be used. The child may be light sensitive and so, tinted glasses may be of very good help. [Sisodiya et al 2005]

Inheritance of microphthalmia

Isolated microphthalmia is sometimes inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. In some cases, parents of affected individuals have less severe eye abnormalities. [Billingsley et al 2006]

When microphthalmia occurs as a feature of a genetic syndrome or chromosomal abnormality, it may cluster in families according to the inheritance pattern for that condition, which may be autosomal recessive or other patterns.

Often microphthalmia is not inherited, and there is only one affected individual in a family. [Bessant et al 1998]