Genes related to inherited microphthalmia and anophthalmia

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Abstract

Congenital eye malformations are the second most common cause of childhood blindness and are originated by disruption of the normal process of eye development during embryonic stage. Their etiology is variable, although monogenic causes are of great importance as they have a high risk of familial recurrence. Included among the most severe congenital eye abnormalities are microphthalmia, defined by an abnormally small eye, and anophthalmia, characterized by congenital absence of ocular structures. The current knowledge of the genes involved in human microphthalmia and anophthalmia in humans is revised in this work.


Congenital eye malformations

Alteration or disruption of any of the numerous processes involved in early development of the eye in humans originate a broad spectrum of congenital eye malformations. Although eye malformations can occur as part of complex genetic syndromes, frequently they are observed in isolation, indicating the disruption of a development process that is exclusive to the eye1,2. On the other hand, the degree of visual impairment associated with these anomalies is variable and depends on the seriousness of the malformation. The etiology of these malformations is complex and can include environmental or genetic factors or a combination of both. Environmental causes can correspond to chemical, biological or physical teratogenic agents that interrupt eye normal development3. Genetic factors associated with malformations can be of three types: multifactorial, chromosomal and monogenic. The most common congenital eye malformation etiology is considered to be the multifactorial one, where the combination of numerous variants in different genes with environmental-type factors is synergistic to originate the malformation. In general, multifactorial and chromosomal alterations have low risk if being inherited by the offspring. The monogenic etiology (also called Mendelian) refers to diseases caused by mutation in a single gene. In these cases there is high risk of repetition in relatives of an affected individual4,5. Monogenic etiology eye malformations are transmitted to the offspring with autosomal dominant, autosomal recessive, X-linked recessive or X-linked dominant patterns. Congenital eye malformations with higher clinical repercussion include microphthalmia and anophthalmia1,6.

Microphthalmia

Microphthalmia is defined as an eye with an axial length two standard deviations below average-for-age, measured by ultrasound7. Microphthalmia can occur unilaterally or bilaterally, and in the unilateral cases, the compromised side of the face is generally less developed and the orbit is small8 (Fig. 1).

Microphthalmia can be associated with other ocular or extraocular congenital anomalies. Some cases of microphthalmia can be associated with an eye cyst
(cystic microphthalmia), which is thought to be the result of a failure in optic fissure closure\(^7\)-10.

**Anophthalmia**

The most serious eye malformation is anophthalmia, which is defined by the absence of the eye globe with preservation of the ocular appendages (eyelids and lacrimal ducts) (Fig. 2). In some cases, recognizing ocular tissue is possible only from the histological point of view\(^11\). In primary anophthalmia, prosencephalon development is suppressed, which results in the absence of one or both eyes, whereas in secondary anophthalmia, the development of the eye is interrupted at the beginning of the fourth week and it is due to a failure in the formation of the lens vesicle\(^12\),13.

**Genes implicated in the development of microphthalmia and anophthalmia**

In the past few years, different genes whose mutations are the cause of a broad spectrum of eye malformations in humans have been identified\(^14\),\(^15\). Mutations in these genes have been found to explain from 18 to 25% of microphthalmia and anophthalmia cases.

| Table 1. Genes related to the development of microphthalmia and anophthalmia |
|-------------------------------|-----------------|---------------------------------|
| **Eye malformation** | **Related genes** |
| Microphthalmia | SOX2, SIX3, OTX2, RAX, CHX10, GDF6, FOXE3, GDF3, STRA6 |
| Anophthalmia | ALDH1A3, ATOH7, RARB and PAX6 |

| Table 2. Localization of genes implicated in anophthalmia and microphthalmia |
|-------------------|-----------------|---------------------------------|
| **Gene** | **Locus (location)** | **Human ocular phenotype** |
| SOX2 | 3q26.3-q27 | Anophthalmia/microphthalmia |
| OTX2 | 14q22 | Anophthalmia/microphthalmia |
| RAX | 18q21.3 | Anophthalmia/microphthalmia |
| SIX3 | 2p21 | Anophthalmia/microphthalmia |
| STRA6 | 15q24.1 | Anophthalmia |
| ALDH1A3 | 15q26 | Microphthalmia |
| ATOH7 | 10q22.2 | Microphthalmia |
| RARB | 3p24 | Anophthalmia/microphthalmia |
| PAX6 | 11p13 | Anophthalmia/microphthalmia |
| CHX10 | 14q24.3 | Microphthalmia |
| GDF6 | 8q22 | Microphthalmia |
| FOXE3 | 1p32 | Microphthalmia |
| GDF3 | 12p13 | Microphthalmia |

In the following sections, the most important features of these genes are described (Tables 1 and 2).

**SOX2**

SOX2, localized in chromosome 3q26, is the most important gene of this group, since its mutations are estimated to be the cause of approximately 10 to 20% of anophthalmia mas bilateral microphthalmia cases\(^16\),17. SOX2 encodes a transcription factor with an essential function in embryonic development in numerous tissues, including the eye and the brain. It acts cooperatively with PAX6 to regulate other genes that promote the development of the lens\(^16\),18, and different dominant mutations of this gene have been described in subjects with anophthalmia or microphthalmia, including point mutations and complete or partial deletions\(^19\). One of the mutations most commonly identified and that corresponds to a deletion of 20 bases at the 5′ extreme of the gene was initially described in Mexican patients with anophthalmia\(^20\),22. Some patients with mutation in SOX2 develop the so-called SOX
deficiency syndrome, which, in addition to eye malformations, includes intellectual impairment, neurological anomalies, facial dysmorphias, postnatal growth retardation, esophageal anomalies and cryptorchidism.23,24

**OTX2**

The OTX2 gene, located at 14q22, encodes a transcription factor that is necessary for cephalic structures embryonic development in vertebrates.21 Different dominant mutations have been described in this gene in patients with anophthalmia or microphthalmia associated with central nervous system malformations and intellectual disability, although cases with retinal dysplasia have been identified as well.29 Approximately 3% of anophthalmia/midrophthalmia cases are due to mutations in OTX2.14

**RAX**

RAX, located at 18q21.32, is another essential gene for ocular development, possibly due to its function in the establishment and proliferation of retinal progenitor cells.30 Around 2% of subjects with anophthalmia or microphthalmia carry mutations in RAX.31,32 Unlike the previously mentioned genes, RAX gene mutations follow an autosomal recessive inheritance pattern.

**SIX3**

The SIX3 gene is located at 2p21 and is crucial in embryonic development, since it intervenes in the anterior brain and eye formation. It encodes a protein with transcription factor function that binds to DNA specific sequences and represses Wnt1 gene activity, an event that ensures normal cerebral development in mammals.33 By blocking Wnt1 gene activity, SIX3 is able to prevent hindbrain abnormal expansion in the forebrain zone. During retinal development, SIX3 has been shown to have a key function in PAX6 activation to promote the lens development.34,35 In addition, SIX3 plays a strategic role in SOX2 activation.36 Mutations in SIX3 also cause serious cerebral malformations, such as type 2 holoprosencephaly (HPE2).37 In HPE2, the brain is unable to separate in two hemispheres during early embryonic development, which drives to eye malformations (including cyclopia) and serious facial abnormalities.38 Mutations in the SIX3 gene follow an autosomal recessive inheritance pattern.

**STRA6**

STRA6 (a retinoic acid-stimulated gene) encodes a protein of the same name that acts as a cell receptor to capture and transport retinol to specific tissues, mainly the eye.39,40 STRA6 is located in chromosome 15q24.1, and its mutations originate anophthalmia, heart defects, pulmonary hypoplasia and diaphragmatic hernia,41,42 which indicates the importance of this gene in normal embryonic development.

**ALDH1A3**

ALDH1A3 encodes aldehyde dehydrogenase 1 A3 isofrom, which is involved in the synthesis of retinoic acid through retinaldehyde oxidation and thus it has an essential function during the eye’s early development.43 The ALDH1A3 gene is located at chromosome 15q26.3 and, recently, its mutations have been shown to be the cause of autosomal recessive inheritance microphthalmia and anophthalmia.44,45

**ATOH7**

The ATOH7 gene (atohal 7 homologous) encodes a helix-loop-helix-type protein and plays an important role in retinal ganglion cell subsets differentiation.46 ATOH7 is located at 10q21.3, and mutations have been recently identified in patients with microphthalmia and other eye development anomalies, such as persistent hyperplastic primary vitreous.47,48

**RARB**

The retinoic acid receptor beta gene (RARB) is a member of the thyroid and steroid hormone nuclear receptors superfamily. The RARB protein binds to retinoic acid, which acts as a cell signaling intermediary in embryonic morphogenesis, cell growth and ocular differentiation processes.50 Recently, using a whole exome sequencing approach, different mutations in this gene were identified in subjects with unilateral or bilateral microphthalmia.51

**PAX6**

PAX6 is known as a “master gene” of eye development, since it intervenes at early and final stages of ocular morphogenesis, neural differentiation and synaptic connections configuration.52,53 PAX6 is located...
at chromosome 11p13, and is widely expressed in the optic vesicle, the lens, the retina and the cornea during ocular development. Typically, \textit{PAX6} mutations cause bilateral aniridia, although certain mutations have also been associated with a broader spectrum of ocular and cerebral defects. Cases of anophthalmia have been identified with mutations in \textit{PAX6}.

\textbf{VSX2}

This gene, also known as \textit{CHX10}, is located at 14q24 and encodes a protein that enables the proliferation of neuroretinal precursor cells. The eye phenotype associated with \textit{VSX2} mutations is heterogeneous, since cases of microphthalmia, coloboma or cataracts have been described. Approximately 2% of subjects with microphthalmia exhibit recessive mutations in \textit{VSX2}. However, in a recent study in 50 Mexican subjects with anophthalmia or microphthalmia, no mutations were identified in this gene, which indicates that there are ethnic variations in the mutation frequencies of genes associated with eye malformations.

\textbf{GDF6}

\textit{GDF6}, located at 8q22, encodes a member of the bone morphogenic proteins family, and is the cause of up to 8% of congenital eye malformation cases, in particular microphthalmia and coloboma. In addition to eye malformations, some patients with dominant mutations in this gene show skeletal alterations and polydactyly, which indicates the importance of \textit{GDF6} gene in different aspects of early embryonic development.

\textbf{FOXE3}

The \textit{FOXE3} gene, located at 1p32, encodes an eye development-specific transcription factor that is highly preserved in phylogeny. Mutations in \textit{FOXE3} originate a broad spectrum of eye malformations, including anterior sector anomalies, congenital aphakia, sclerocornea, cataracts and microphthalmia. In a recent study, approximately 25% of subjects with microphthalmia had recessive mutations in \textit{FOXE3}. One interesting aspect of this gene is that its heterozygous (dominant) mutations have been also associated with eye anomalies, such as chorioretinal and iris colobomas, Peters’ anomaly and early-onset cataracts. In an analysis of 236 subjects with developmental eye anomalies, two new heterozygous mutations of \textit{FOXE3} were identified, which dominantly segregated into two different families. By means of in situ hybridization in human embryos, \textit{FOXE3} expression was shown to be exclusive of the eye, mainly in the anterior segment, which suggests that the extralenticular phenotypes caused by mutations in \textit{FOXE3} are probably secondary to the formation of abnormal lenses.

\textbf{GDF3}

\textit{GDF3} is a gene located at 12p13.1 that codifies a protein belonging to the bone morphogenetic proteins family, which participate in a wide variety of processes during embryonic development. In a group of 33 patients with eye malformations, four cases with dominant mutations in \textit{GDF3} and a broad spectrum of eye malformations, ranging from iris coloboma to bilateral microphthalmia, were identified. Interestingly, evidence was found of lack of penetrance of some of these mutations. \textit{GDF3} has been estimated to be mutated in approximately 2% of patients with the microphthalmia-anophthalmia-coloboma and thus should be included as one of the genes to be analyzed in subjects with congenital eye malformations.

\textbf{Final considerations}

In the past few years, genes whose mutations originate a broad spectrum of eye malformations in the human being have been identified. Subsequently, functional, expression and animal model studies have confirmed the participation of these genes in the pathways of eye normal development. Availability of new technologies, such as whole genome sequencing and whole exome sequencing, have significantly increased the capability to identify new genes related to this type of inherited anomalies. In addition to establishing the malformation specific cause, which is information that is highly valuable to the patient and his/her family, one of the goals of the genetic studies in patients with eye malformations is to estimate the mutation frequency of each gene in specific ethnic groups. This information is highly relevant for genotyping better planning in new cases, to better understanding these malformations’ physiopathogenesis and for adequate genetic counseling of affected subjects’ families.
References


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