Chapter 9
Vertebrate Eye Gene Regulatory Networks

Juan R. Martinez-Morales

Abstract The development of the eye in vertebrates entails the precise coordination of the genetic programs that control morphogenetic movements and inductive signals. The basic blueprint of the vertebrate eye is established in the developmental window comprised between the specification of the eye field at early gastrulation and the onset of neuronal differentiation (Martinez-Morales and Wittbrodt in Curr Opin Genet Dev 19(5):511–517, 2009; Fuhrmann in Curr Top Dev Biol 93:61–84, 2010; Sinn and Wittbrodt in Mech Dev 130(6–8):347–358, 2013). During this period, the precursor cells from the eye primordium get specified, and then differentiate to form three major tissue domains: the neural retina, the retinal-pigmented epithelium (RPE), and the optic stalk domains. A process that culminates with the formation of the optic cup, a highly conserved embryonic structure that represents a common arrangement for the embryonic eye in vertebrates (Tena et al. in Genome Res, 2014). This chapter will focus in the architecture of the Gene Regulatory Networks (GRNs) during early organogenesis. The structure of the GRNs involved in the initial specification and differentiation of the major non-neural component of the eye, the lens, will not be examined here. The reader is referred to the following reviews for a detailed discussion on this subject (Cvekl and Duncan in Prog Retin Eye Res 26(6): 555–597, 2007; Cvekl and Ashery-Padan in Development 141(23):4432–4447, 2014).

Keywords Eye field specification · Neural retina · Retinal-pigmented epithelium · Optic stalk · Optic cup patterning

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9.1 Introduction

9.1.1 GRNs Specifying the Eye Morphogenetic Field

Under the influence of signals determining the mayor embryo axes (WNTs, BMPs, Nodal and FGFs), a large group of cells in the anterior neural plate gets specified as presumptive eye tissue (Wilson and Houart 2004). Classical explant experiments in salamanders have shown that, even before this region evaginates to form the optic vesicles, it is already committed and will develop as an optic cup when cultured in vitro (Lopashov and Stroeva 1964). Early expressed in this territory, a number of transcription factor-encoding genes (known as eye field transcription factors or EFTFs) have been acknowledged as the molecular signature defining the identity of the tissue. These include homeobox genes such as *Rx*, *Pax6*, *Six3*, *Lhx2*, or *Six6*. Among them, especially *Rx*, *Pax6* and *Six3* are essential for eye formation in all vertebrate models analysed (Sinn and Wittbrodt 2013). The fact that eye specification in *Drosophila* also depends on *eyeless*, *twin of eyeless* (both homologous of *Pax6*) and *sine oculis* (homologous of *Six3* and *Six6*) suggests a conserved "*Kernel*" for the development of the eye field in bilaterians (Davidson and Erwin 2006; Wagner 2007). Although it seems clear that vertebrate EFTFs constitute central nodes of a complex GRN, their precise hierarchical relationships are still poorly understood. The miss-expression of a few eye specification genes, such as *Six3* and *Pax6,* is sufficient to induce the ectopic expression of eye tissues in vertebrates (Chow et al. 1999; Loosli et al. 1999; Zuber et al. 1999; Lagutin et al. 2001). While this fact points to a top hierarchical position for both genes in a "linear GRN model", it is very likely that the network's assembly is more complex and multiple steps of feedback regulation exist, as previously reported for eye specification in *Drosophila* (Treisman 1999; Kumar and Moses 2001). Thus, it has been shown that the miss-expression of *Six3* or *Pax6* mRNAs recruits other eye specification genes, and that the co-expression of EFTF cocktails acts as a much more potent inducer than that of single genes, being sufficient to induce ectopic eyes outside the nervous system (Zuber et al. 2003) and to instruct pluripotent cells into the eye developmental program (Viczian et al. 2009). Interestingly, these studies also showed that EFTF cocktails' efficiency to induce ectopic eyes largely depended on the inclusion of *Otx2* in the mixture (Zuber et al. 2003). This is in agreement with previous reports showing the important role of ***Otx*** genes in eye formation (Matsuo et al. 1995; Martinez-Morales et al. 2001), and with the observation that ectopic eye induction mediated by *Pax6* or *Six3* is restricted to the *Otx* expression domain (Chow et al. 1999; Loosli et al. 1999).

An attempt to define the regulatory relationships among nodes (i.e. the genes and their regulators) at the core of the eye field GRN has been carried out in Xenopus (Zuber et al. 2003). In this report EFTFs regulatory interactions were tested in overexpression experiments and a tentative GRN, comparable to that proposed for *Drosophila* eye development, was deduced (Fig. 9.1). Several predictions from this model were consistent with hierarchical relationships found in *Xenopus* and other

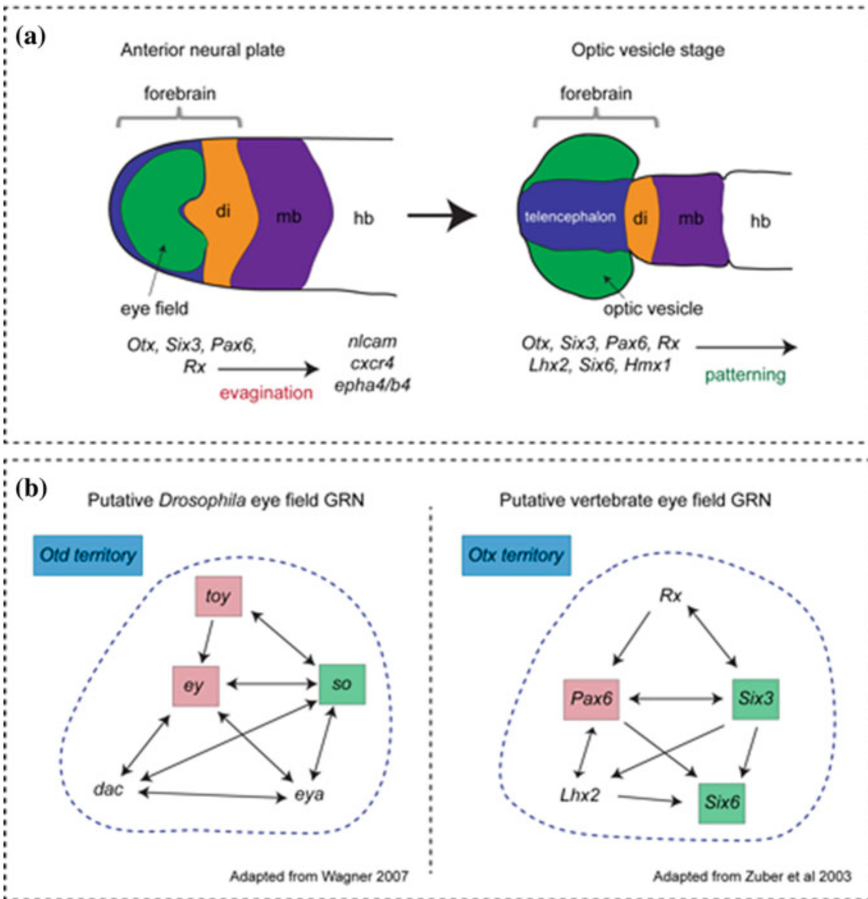

Fig. 9.1 GRNs specifying the eye morphogenetic field: **a** Schematic representation of anterior neural plate domains (*color-coded*) during eye field specification and optic vesicle evagination stages. Relevant transcription factors, downstream genes and morphogenetic processes are indicated. **b** Hypothetical eye specification networks are represented for *Drosophila* and vertebrates. Homologous genes are indicated in similar *colored boxes*. *di* diencephalon; *mb* midbrain; *hb* hindbrain

vertebrate models through gain and loss of function experiments. For example, a downstream role for ***Six6/Optx2*** in the GRN specifying the eye field was confirmed (Zuber et al. 1999, 2003; Li et al. 2002). However, although useful as a working model, it should be taken with caution as is merely based on overexpression studies and some of its assumptions have been already proved to be incorrect. This is the case for the prominent position of *Rx*/*Rax* at the top of the hierarchy in the eye GRN. In contrast to the model's prediction, the expression in *Xenopus* of the EFTF (i.e. *Pax6*, *Six3*, *Lhx2*, and *Six6*) seems unaffected at early neurula stage in *Rax* mutant embryos (Fish et al. 2014), thus indicating a downstream role for this gene

in the network. More importantly, there is strong evidence showing that the exact wiring of the eye field GRN varies in different vertebrate groups. With the possible exception of ***Six3***, which seems to occupy a prevalent upstream position by suppressing canonical Wnt signalling anteriorly in all species analysed (Wallis et al. 1999; Carl et al. 2002; Lagutin et al. 2003; Liu et al. 2010; Nakayama et al. 2013), the regulatory weight and hierarchical position of other EFTF differs considerably among species. In some cases, phenotypic discrepancies between mutants in different species can be attributed to the existence of multiple paralogs (i.e. genes related by duplication within a genome) for a given EFTF in the teleost models. This is the case for ***Pax6***, whose inactivation in mouse and Xenopus results in an almost complete loss of the eye territory (Hill et al. 1991; Suzuki et al. 2013), whereas only causes microphthalmia when one of the two *Pax6* paralogs, *pax6b,* is mutated in zebrafish (Kleinjan et al. 2008). Nevertheless, gene duplication cannot always justify the observed phenotypic discrepancies. Thus, in mouse ***Rx*** mutants eye field determinants are down-regulated at very early stages and consistently eye development is impaired even before optic vesicle evagination (Mathers et al. 1997; Zhang et al. 2000; Medina-Martinez et al. 2009), but in Xenopus and teleost fish *Rx* function seems dispensable during eye field specification, being required for optic vesicle evagination and eye identity maintenance later on Loosli et al. (2001, 2003), Rembold et al. (2006) and Fish et al. (2014). Similarly, in ***Lhx2*** mutant mice eye development is arrested prior to the formation of an optic cup (Porter et al. 1997; Tetreault et al. 2009) whereas the homologous mutation in zebrafish (*belladonna*) displays a milder phenotype affecting the patterning of the ventral forebrain and eye (Seth et al. 2006). An extreme example of functional divergence among vertebrate species is the case of the transcription factor ***ET/Tbx2***, which appears to play a central role during eye field specification in Xenopus (Zuber et al. 2003), but its loss of function only causes a mild microphthalmia in mice (Behesti et al. 2009).

In summary, the existence of cooperative effects, feedback regulatory loops, and species-specific wiring hinders the definition of a precise architecture for the core GRN involved in vertebrate eye specification. Even less information is available on the structure of the downstream layer of the network. Yet, it is likely that this sub-network includes genes controlling optic vesicle evagination. In tetrapods, the anterior neural tube develops as a hollow structure and vesicle evagination occurs by lateral bulging of the neuroepithelium (Hilfer 1983; Eiraku et al. 2011). In contrast, the neural tube develops as a compact tissue in teleosts, and the formation of the optic vesicle requires the migration, rearrangement and epithelialization of individual precursors (England et al. 2006; Rembold et al. 2006; Ivanovitch et al. 2013). A few downstream targets of *rx3*: *nlcam*, *cxcr4* and *epha4a*/*b4b* have been shown to control the migratory and adhesive behaviour of the eye field precursors as optic vesicle evaginate in zebrafish (Brown et al. 2010; Bielen and Houart 2012; Cavodeassi et al. 2013). In spite of these advances, systematic attempts to identify potential downstream targets of the EFTF have not been carried out until recently, either by exploring the eye field transcriptome (Viczian et al. 2009), or by interrogating the network structure upon mutation of *rx3* using an RNA-seq approach

(Yin et al. 2014). The emergence of the powerful next-generation sequencing technologies coupled to ChIP methods has allowed the identification of cis-regulatory modules at a genome scale (ENCODE_Project_Consortium et al. 2012). The enormous potential of these approaches to investigate the complexity of the GRNs involved in eye development has just started to be explored. A couple of studies have been carried out to systematically characterize cis-regulatory modules occupied by Otx2, during gastrulation in Xenopus and in the adult mouse retina (Samuel et al. 2014; Yasuoka et al. 2014). Additional ChIP-seq studies focused on other EFTF will be instrumental not only to clarify the wiring diagram of the core eye field GRN, but also to infer direct cis-regulatory targets of these transcription factors.

9.1.2 GRNs Specifying Eye Domains

Once the eye morphogenetic field is specified, signalling molecules derived from the retina and neighbouring tissues act to restrict the precursors' potentiality, subdividing the optic vesicle into three regions: the neural retina, the retinal pigmented epithelium (RPE) and the optic stalk.[1] Inductive signals include SHH and nodal secreted from the CNS midline, FGFs from the retina and the presumptive lens ectoderm, and activins, Wnts, and BMPs from the extraocular mesenchyme and the dorsal ectoderm; which specify the optic stalk, the neural retina and the RPE respectively (Adler and Canto-Soler 2007; Martinez-Morales et al. 2009; Fuhrmann 2010; Steinfeld et al. 2013) (Fig. 9.2). At early stages, vertebrate eye subdivisions cannot be considered tissue compartments in the strict sense of the term, as transfer of precursor cells has been reported between different domains (Holt 1980; Picker et al. 2009; Kwan et al. 2012). Thus, limits between territories are initially dynamic, and depend on sustained signalling input that maintains tissue identity by regulating domain-specific transcription factors. By the time the optic cup has folded, ocular tissues are stabilized into genuine compartments (i.e. with defined borders and no cellular intermingling) through reciprocal transcriptional repression. Some examples of mutual transcriptional repression contributing to border definition have been reported. They include *Pax2*/*Pax6* and *Mitf*/*Vsx2* antagonism that participate in the definition of the optic stalk/neural retina and RPE/neural retina borders respectively (Schwarz et al. 2000; Horsford et al. 2005; Bharti et al. 2008).

The development of the different eye tissues entails the bifurcation of the eye field specification GRN into mutually exclusive developmental programs controlled by local sub-networks. This process translates into distinctive cell morphologies within each domain: flat for the RPE, and long or short bottle-shaped for the neural

[1]For the sake of simplicity, the development of the optic disc and the ciliary body (i.e. the specialized structures differentiating at the interface between the main retinal domains) will not be discussed in this chapter.

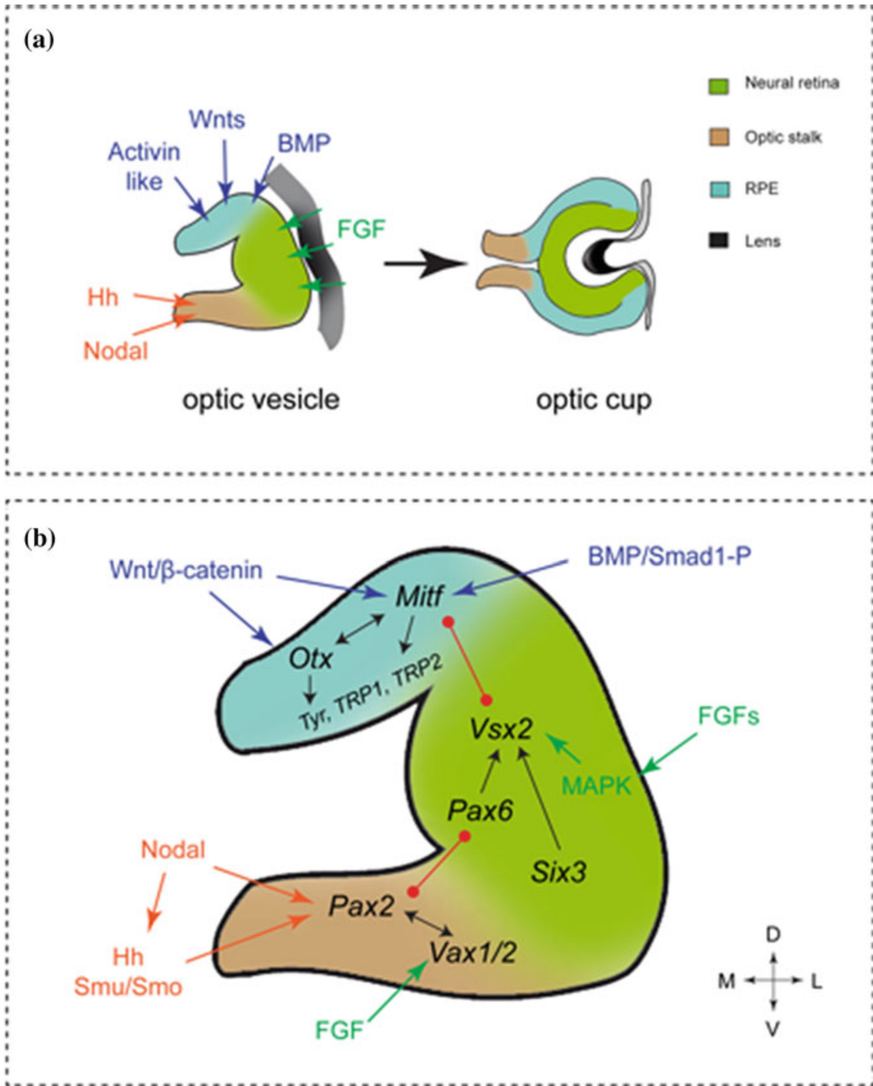

Fig. 9.2 GRNs specifying eye domains: **a** signaling molecules derived from the presumptive lens ectoderm (*grey*), the midline and the dorsal ectoderm/mesoderm pattern the optic vesicle into the neural retina (*green*), optic stalk (*brown*) and RPE (*blue*) domains. **b** Hypothetical GRNs specifying each retinal domain are depicted. Transcriptional regulators and known downstream targets are represented in *black*. Signaling pathways are *color-coded*. Repressive interactions are represented in *red*

retina or optic stalk respectively. These differential cell geometries, established within a few hours window, will condition the morphogenetic movements that take place during optic cup invagination. Thus RPE and neural retina epithelia fold over

the lens vesicle to form a bi-layered cup and optic stalk lips converge ventrally to close the choroid fissure groove (Martinez-Morales et al. 2009; Eiraku et al. 2011; Kwan et al. 2012). Each of the ocular domains retains during embryogenesis certain potentiality for transdifferentiation into a different compartment (Coulombre and Coulombre 1965; Pittack et al. 1991; Guillemot and Cepko 1992; Turque et al. 1996; Vogel-Hopker et al. 2000; Rowan and Cepko 2004). As organ development proceeds and retinal domains progressively acquire divergent morphological and physiological features (e.g. pigmentation, glial and neuronal cell types, etc.), potentiality is lost and the competence for transdifferentiation in the adult is only maintained in amphibians (Del Rio-Tsonis and Tsonis 2003; Fuhrmann et al. 2014).

Although much has been advanced in the last years, our knowledge on the structure of the GRNs that control the developmental programs of the neural retina, RPE and optic stalk is still fragmentary and even the precise relationships among the top upstream genes of these networks are unclear. Here, we summarize the main findings for each of the three ocular domains.

Neural retina GRN: At the end of the evagination process, the optic vesicle comprises two *back-to-back* epithelial layers: an outer layer (dorsal in teleost fish) apposed to the presumptive lens ectoderm, and an inner layer (ventral in teleosts) surrounded by mesenchymal tissue. These two layers initially similar in size and volume will differentiate to generate a thick neural retina, and a thin RPE (Svoboda and O'Shea 1987; Li et al. 2000). The neural retina specification network pivots on the transcription factor-encoding gene *Vsx2*, also known as *Chx10*, which is the first determination gene differentially expressed in the presumptive neural retina versus the presumptive RPE (Liu et al. 1994). A number of reports have shown that *Vsx2* has an essential role in the specification of the retinal domain, restraining RPE identity (i.e. RPE specific GRN) through direct repression of the transcription factor *Mitf* (Rowan and Cepko 2004; Horsford et al. 2005; Bharti et al. 2008; Zou and Levine 2012). *Vsx2* activity seems to be required for the maintenance of a neural retina specific GRN, whose main regulators (nodes) are inherited core components of the eye field GRN, including *Rx*, *Pax6*, *Six3* and *Six6* (Medina-Martinez et al. 2009; Fuhrmann 2010; Bharti et al. 2012).

FGFs derived from the presumptive lens ectoderm play a fundamental role in positioning the neural retina at the expenses of the RPE territory (Guillemot and Cepko 1992; Pittack et al. 1997; Hyer et al. 1998; Vogel-Hopker et al. 2000; Cai et al. 2010). Thus, FGF signalling acts to suppress the gene encoding for RPE transcription factor Mitf while activating the neural retina determinant *Vsx2*, setting up the boundary between both tissues (Nguyen and Arnheiter 2000; Horsford et al. 2005). Several laboratories have dissected the signalling cascade responsible for this inductive activity, which operates through the Shp2/MEK/ERK pathway (Zhao et al. 2001; Galy et al. 2002; Cai et al. 2010). Interestingly, the well-described trans-differentiation of the RPE to neural retina by FGF does not occur in null mutant mice for *Vsx2* (Horsford et al. 2005). Thus, *Vsx2* seems to be a direct target of the FGF/ERK pathway and *Mitf* repression by FGF depends on *Vsx2* function.

The precise regulatory relationships between the core components of the neural retina specification network (i.e. *Vsx2*, *Pax6*, *Six3*, *Six6*; and *Rx*) are currently

unclear. However, some of the downstream targets of the network have been inferred by transcriptomic analyses in *Vsx2* knockout models, as well as in *Vsx2−/−* induced pluripotent stem cells (Rowan and Cepko 2004; Phillips et al. 2014). Again, RNA-seq and ChIP-seq technologies will be instrumental to identify more components of this GRN and to investigate systematically the wiring scheme of its core components.

Retinal Pigmented Epithelium GRN: The RPE is a highly specialized monolayered epithelium essential for the correct development and homeostasis of the adjacent neural retina (Raymond and Jackson 1995; Strauss 2005). Establishment of the RPE gene regulatory network depends on the cooperative activity of two core transcriptional regulators: *Mitf* and the *Otx* family members *Otx1* and *Otx2* (Martinez-Morales et al. 2004; Fuhrmann et al. 2014). *Mitf* encodes a basic helix-loop-helix (bHLH) transcription factor that plays a key role as master regulator of pigmented cell specification, both in melanocytes and retinal neuroepithelial cells (Hodgkinson et al. 1993; Steingrimsson et al. 2004; Arnheiter 2010). *Mitf* loss-of-function impairs the correct specification of the presumptive epithelium, which remains un-pigmented and develops as a pseudo-stratified neuroepithelium (Mochii et al. 1998; Nakayama et al. 1998; Bumsted and Barnstable 2000; Nguyen and Arnheiter 2000). Conversely, *Mitf* gain of function enhances the RPE regulatory network, and in certain genetic background mediates the transdifferentiation of the neural retina into pigmented cells (Planque et al. 1999; Horsford et al. 2005). Similarly, *Otx* genes are early restricted to the RPE territory during optic cup stages and are required to establish the identity of this tissue (Bovolenta et al. 1997; Martinez-Morales et al. 2001; Lane and Lister 2012). The expression of *Mitf* and *Otx* genes in the presumptive RPE depends on their reciprocal activity, and both cooperate to induce a pigmented phenotype interacting directly at the protein level (Martinez-Morales et al. 2003; Lane and Lister 2012). Both transcription factors have been shown to operate directly on the direct downstream effectors of the pigmentation cascade. Thus, Mitf and Otx proteins activate the transcription of melanogenic genes such as *QNR71*, *Tyrosinase*, *TRP1* and *TRP2,* acting synergistically through their consensus motives, CATGTG (M-box) and TAATCC/T (K50-type homeodomain), respectively (Goding 2000; Martinez-Morales et al. 2003). Interestingly, it has been shown that *Pax6* activity, normally associated to the development of the neural retina, is essential for the establishment of the RPE identity in conjunction with *Mitf* (Baumer et al. 2003; Bharti et al. 2012). The establishment and maintenance of the RPE regulatory network depends on the inductive activity from surrounding tissues, including the extraocular mesenchyme and the surface ectoderm. Among the inductive signals, activins derived from the mesenchyme (Fuhrmann et al. 2000) as well as BMPs and Wnts from the dorsal ectoderm (Hyer et al. 2003; Muller et al. 2007; Steinfeld et al. 2013) control the differentiation of the RPE.

As previously discussed for eye field specification (see previous section), species-specific differences in the architecture of the pigmented epithelium GRN have been documented among vertebrate groups. Thus, in teleosts *Mitf* seems to have a less important regulatory weight in RPE determination, being the regulatory

network more dependent on *Otx* (Lane and Lister 2012). Divergent regulation has also been reported for inductive signalling. In mice Wnt-dependent RPE specification has been characterized as a β-catenin dependent process that involves the direct activation of TCF/LEF sites in *Mitf* and *Otx2* enhancers (Fujimura et al. 2009; Westenskow et al. 2009). In contrast, RPE induction in chicken requires the cooperative activity of Wnt and BMP signalling through a GSK3β-pSmad pathway (Steinfeld et al. 2013).

Optic stalk (OS) GRN: As eye development proceeds precursor cells from the optic vesicle differentiate in two fundamentally different populations. Those precursors located proximally to the midline will give rise to the OS, whereas more distal cells will form the optic cup, including the neural retina and RPE domains (Peters 2002). Eventually, optic stalk cells undertake the differentiation program that leads to the formation of the optic nerve. This local GRN is established under the influence of signalling molecules that emanate from the midline and pattern the optic vesicles along the proximo-distal axis. Nodal, hedgehog (Hh), and FGF signalling pathways have been identified as positive signals for the establishment and maintenance of the OS developmental program, while restricting distal BMP inducers (Peters 2002). Nodal family members, such as *one-eyed pinhead* (*oep*) and *cyclops*, play an essential role in patterning the central nervous system ventral midline (Rebagliati et al. 1998; Sampath et al. 1998). Mutations in genes encoding for these TGFβ related ligands result in cyclopic defects and loss of midline identity markers, particularly Hh (Macdonald et al. 1995; Rohr et al. 2001). Hh, acting as a morphogen, is necessary to induce the expression in the proximal optic vesicle of the key nodes of the OS GRN, *Pax2*, *Vax1* and *Vax2* (see below) both in mammals and teleost models (Ekker et al. 1995; Macdonald et al. 1995; Chiang et al. 1996). Modifiers of Hh proximo-distal signalling help to define the morphogen influence domain in the ventral optic vesicle (Lee et al. 2008; Cardozo et al. 2014). In addition to axial signalling, other independent pathways active in the ventral optic vesicle, such as FGFs and retinoic acid, have been shown to regulate the expression of OS specification genes (Take-uchi et al. 2003; Lupo et al. 2005; Cai et al. 2013).

The core GRN for OS identity comprises three homebox-encoding genes *Pax2* (Torres et al. 1996; Macdonald et al. 1997), *Vax1* and *Vax2* (Barbieri et al. 1999, 2002; Bertuzzi et al. 1999; Mui et al. 2005; Kim and Lemke 2006). Their mutations result in OS impaired development and hence are associated to coloboma, choroid fissure malformations and axonal guidance defects. Although most of the downstream targets of this core network need to be identified, the segregation of the optic cup and OS domains depends on the repression of *Pax6*, a central node in the specification of both the neural retina and the RPE territories (Schwarz et al. 2000; Mui et al. 2005; Bharti et al. 2012).

As already mentioned, the bifurcation of the eye field specification GRN into domain-specific developmental programs has a direct impact in the acquisition of defined cell morphologies within each compartment. However, very little is known on the molecular machineries controlling these morphogenetic processes. In fact, understanding how a particular GRN unfold may require the identification of its downstream targets. These, operating under the control of the master regulators,

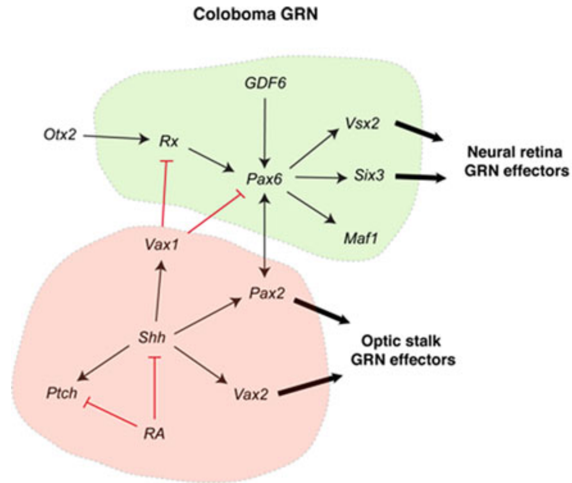

Fig. 9.3 Coloboma gene network: genes mutated in human families affected by Microphthalmia, Anophthalmia, and Coloboma (MAC) are depicted in this network. Neural retina (*green*) and optic stalk (*red*) specific sub-networks are indicated with different colors. Adapted from Gregory-Evans et al. (2013)

will modify directly basic cell properties such as adhesion, shape and contractility. The *ojoplano* (*opo)* gene, which has an essential role in neural retina morphogenesis by controlling integrin polarized endocytosis, is a paradigmatic example of such type of targets (Martinez-Morales et al. 2009; Bogdanovic et al. 2012). Recent advances in whole-genome transcriptomics and epigenomics open the possibility of systematically surveying for the downstream determinants of cell geometry and epithelial morphogenesis in early eye development.

Finally, most of the important nodes of the GRNs involved in eye domains specification (e.g. *Pax6*, *Vsx2*, *Rx*, *Otx2*, etc.) have also been identified as key nodes of the "coloboma gene network" (Fig. 9.3): i.e. the network of genes that have been found mutated in human families affected by microphthalmia, anophthalmia, and coloboma (MAC) (Gregory-Evans et al. 2004, 2013). Although this group of diseases represents a significant cause of blindness in children (5–10 %) (Porges et al. 1992), its molecular causes are complex and far from being completely understood. Therefore, gaining insight into the architecture of the GRNs involved in eye development has important medical implications.

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References

Adler, R., & Canto-Soler, M. V. (2007). Molecular mechanisms of optic vesicle development: Complexities, ambiguities and controversies. *Development Biology, 305*(1), 1–13.

Arnheiter, H. (2010). The discovery of the microphthalmia locus and its gene, Mitf. *Pigment Cell Melanoma Research, 23*(6), 729–735.

Barbieri, A. M., Broccoli, V., Bovolenta, P., Alfano, G., Marchitiello, A., Mocchetti, C., et al. (2002). Vax2 inactivation in mouse determines alteration of the eye dorsal-ventral axis, misrouting of the optic fibres and eye coloboma. *Development, 129*(3), 805–813.

Barbieri, A. M., Lupo, G., Bulfone, A., Andreazzoli, M., Mariani, M., Fougerousse, F., et al. (1999). A homeobox gene, vax2, controls the patterning of the eye dorsoventral axis. *Proceedings of the National Academy of Sciences of the United States of America, 96*(19), 10729–10734.

Baumer, N., Marquardt, T., Stoykova, A., Spieler, D., Treichel, D., Ashery-Padan, R., et al. (2003). Retinal pigmented epithelium determination requires the redundant activities of Pax2 and Pax6. *Development, 130*(13), 2903–2915.

Behesti, H., Papaioannou, V. E., & Sowden, J. C. (2009). Loss of Tbx2 delays optic vesicle invagination leading to small optic cups. *Developmental Biology, 333*(2), 360–372.

Bertuzzi, S., Hindges, R., Mui, S. H., O'Leary, D. D., & Lemke, G. (1999). The homeodomain protein vax1 is required for axon guidance and major tract formation in the developing forebrain. *Genes & Development, 13*(23), 3092–3105.

Bharti, K., Gasper, M., Ou, J., Brucato, M., Clore-Gronenborn, K., Pickel, J., et al. (2012). A regulatory loop involving PAX6, MITF, and WNT signaling controls retinal pigment epithelium development. *PLoS Genetics, 8*(7), e1002757.

Bharti, K., Liu, W., Csermely, T., Bertuzzi, S., & Arnheiter, H. (2008). Alternative promoter use in eye development: The complex role and regulation of the transcription factor MITF. *Development, 135*(6), 1169–1178.

Bielen, H., & Houart, C. (2012). BMP signaling protects telencephalic fate by repressing eye identity and its Cxcr4-dependent morphogenesis. *Developmental Cell, 23*(4), 812–822.

Bogdanovic, O., Delfino-Machin, M., Nicolas-Perez, M., Gavilan, M. P., Gago-Rodrigues, I., Fernandez-Minan, A., et al. (2012). Numb/Numbl-Opo antagonism controls retinal epithelium morphogenesis by regulating integrin endocytosis. *Developmental Cell, 23*(4), 782–795.

Bovolenta, P., Mallamaci, A., Briata, P., Corte, G., & Boncinelli, E. (1997). Implication of *Otx2* in pigmented epithelium determination and neural retina differentiation. *Journal of Neuroscience, 17*, 4243–4252.

Brown, K. E., Keller, P. J., Ramialison, M., Rembold, M., Stelzer, E. H., Loosli, F., et al. (2010). Nlcam modulates midline convergence during anterior neural plate morphogenesis. *Developmental Biology, 339*(1), 14–25.

Bumsted, K. M., & Barnstable, C. J. (2000). Dorsal retinal pigment epithelium differentiates as neural retina in the microphthalmia (mi/mi) mouse. *Investigative Ophthalmology & Visual Science, 41*(3), 903–908.

Cai, Z., Feng, G. S., & Zhang, X. (2010). Temporal requirement of the protein tyrosine phosphatase Shp2 in establishing the neuronal fate in early retinal development. *Journal of Neuroscience, 30*(11), 4110–4119.

Cai, Z., Tao, C., Li, H., Ladher, R., Gotoh, N., Feng, G. S., et al. (2013). Deficient FGF signaling causes optic nerve dysgenesis and ocular coloboma. *Development, 140*(13), 2711–2723.

Cardozo, M. J., Sanchez-Arrones, L., Sandonis, A., Sanchez-Camacho, C., Gestri, G., Wilson, S. W., et al. (2014). Cdon acts as a Hedgehog decoy receptor during proximal-distal patterning of the optic vesicle. *Nature Communications, 5*, 4272.

Carl, M., Loosli, F., & Wittbrodt, J. (2002). Six3 inactivation reveals its essential role for the formation and patterning of the vertebrate eye. *Development, 129*(17), 4057–4063.

Cavodeassi, F., Ivanovitch, K., & Wilson, S. W. (2013). Eph/Ephrin signalling maintains eye field segregation from adjacent neural plate territories during forebrain morphogenesis. *Development, 140*(20), 4193–4202.

Chiang, C., Litingtung, Y., Lee, E., Young, K. E., Corden, J. L., Westphal, H., et al. (1996). Cyclopia and defective axial patterning in mice lacking Sonic Hedgehog gene function. *Nature, 383*, 407–413.

Chow, R. L., Altmann, C. R., Lang, R. A., & Hemmati-Brivanlou, A. (1999). Pax6 induces ectopic eyes in a vertebrate. *Development, 126*(19), 4213–4222.

Coulombre, J. L., & Coulombre, A. J. (1965). Regeneration of neural retina from the pigmented epithelium in the chick embryo. *Developmental Biology, 12*(1), 79–92.

Cvekl, A., & Ashery-Padan, R. (2014). The cellular and molecular mechanisms of vertebrate lens development. *Development, 141*(23), 4432–4447.

Cvekl, A., & Duncan, M. K. (2007). Genetic and epigenetic mechanisms of gene regulation during lens development. *Progress in Retinal and Eye Research, 26*(6), 555–597.

Davidson, E. H., & Erwin, D. H. (2006). Gene regulatory networks and the evolution of animal body plans. *Science, 311*(5762), 796–800.

Del Rio-Tsonis, K., & Tsonis, P. A. (2003). Eye regeneration at the molecular age. *Developmental Dynamics, 226*(2), 211–224.

Eiraku, M., Takata, N., Ishibashi, H., Kawada, M., Sakakura, E., Okuda, S., et al. (2011). Self-organizing optic-cup morphogenesis in three-dimensional culture. *Nature, 472*(7341), 51–56.

Ekker, S. C., Ungar, A. R., Greenstein, P., von Kessler, D., Porter, J. A., Moon, R. T., et al. (1995). Patterning activities of vertebrate hedgehog proteins in the developing eye and brain. *Current Biology, 5*, 944–955.

ENCODE_Project_Consortium, Bernstein, B. E., Birney, E., Dunham, I., Green, E. D., Gunter, C., & Snyder, M. (2012). An integrated encyclopedia of DNA elements in the human genome. *Nature, 489*(7414), 57–74.

England, S. J., Blanchard, G. B., Mahadevan, L., & Adams, R. J. (2006). A dynamic fate map of the forebrain shows how vertebrate eyes form and explains two causes of cyclopia. *Development, 133*(23), 4613–4617.

Fish, M. B., Nakayama, T., Fisher, M., Hirsch, N., Cox, A., Reeder, R., et al. (2014). Xenopus mutant reveals necessity of rax for specifying the eye field which otherwise forms tissue with telencephalic and diencephalic character. *Developmental Biology, 395*(2), 317–330.

Fuhrmann, S. (2010). Eye morphogenesis and patterning of the optic vesicle. *Current Topics in Developmental Biology, 93*, 61–84.

Fuhrmann, S., Levine, E. M., & Reh, T. A. (2000). Extraocular mesenchyme patterns the optic vesicle during early eye development in the embryonic chick. *Development, 127*(21), 4599–4609.

Fuhrmann, S., Zou, C., & Levine, E. M. (2014). Retinal pigment epithelium development, plasticity, and tissue homeostasis. *Experimental Eye Research, 123*, 141–150.

Fujimura, N., Taketo, M. M., Mori, M., Korinek, V., & Kozmik, Z. (2009). Spatial and temporal regulation of Wnt/beta-catenin signaling is essential for development of the retinal pigment epithelium. *Developmental Biology, 334*(1), 31–45.

Galy, A., Neron, B., Planque, N., Saule, S., & Eychene, A. (2002). Activated MAPK/ERK kinase (MEK-1) induces transdifferentiation of pigmented epithelium into neural retina. *Developmental Biology, 248*(2), 251–264.

Goding, C. R. (2000). Mitf from neural crest to melanoma: Signal transduction and transcription in the melanocyte lineage. *Genes & Development, 14*(14), 1712–1728.

Gregory-Evans, C. Y., Wallace, V. A., & Gregory-Evans, K. (2013). Gene networks: Dissecting pathways in retinal development and disease. *Progress in Retinal and Eye Research, 33*, 40–66.

Gregory-Evans, C. Y., Williams, M. J., Halford, S., & Gregory-Evans, K. (2004). Ocular coloboma: A reassessment in the age of molecular neuroscience. *Journal of Medical Genetics, 41*(12), 881–891.

Guillemot, F., & Cepko, C. L. (1992). Retinal fate and ganglion cell differentiation are potentiated by acidic FGF in an in vitro assay of early retinal development. *Development, 114*(3), 743–754.

Hilfer, S. R. (1983). Development of the eye of the chick embryo. *Scanning Electron Microscopy,* (Pt 3), 1353–1369.

Hill, R. E., Favor, J., Hogan, B. L. M., Ton, C. C. T., Saunders, G. F., Hanson, I. M., et al. (1991). Mouse small eye results from mutations in a paired-like homeobox containing gene. *Nature, 354*, 522–525.

Hodgkinson, C. A., Moore, K. J., Nakayama, A., Steingrimsson, E., Copeland, N. G., Jenkins, N. A., et al. (1993). Mutations at the mouse microphthalmia locus are associated with defects in a gene encoding a novel basic-helix-loop-helix-zipper protein. *Cell, 74*(2), 395–404.

Holt, C. (1980). Cell movements in Xenopus eye development. *Nature, 287*(5785), 850–852.

Horsford, D. J., Nguyen, M. T., Sellar, G. C., Kothary, R., Arnheiter, H., & McInnes, R. R. (2005). Chx10 repression of Mitf is required for the maintenance of mammalian neuroretinal identity. *Development, 132*(1), 177–187.

Hyer, J., Kuhlman, J., Afif, E., & Mikawa, T. (2003). Optic cup morphogenesis requires pre-lens ectoderm but not lens differentiation. *Developmental Biology, 259*(2), 351–363.

Hyer, J., Mima, T., & Mikawa, T. (1998). FGF1 patterns the optic vesicle by directing the placement of the neural retina domain. *Development, 125*(5), 869–877.

Ivanovitch, K., Cavodeassi, F., & Wilson, S. W. (2013). Precocious acquisition of neuroepithelial character in the eye field underlies the onset of eye morphogenesis. *Developmental Cell, 27*(3), 293–305.

Kim, J. W., & Lemke, G. (2006). Hedgehog-regulated localization of Vax2 controls eye development. *Genes & Development, 20*(20), 2833–2847.

Kleinjan, D. A., Bancewicz, R. M., Gautier, P., Dahm, R., Schonthaler, H. B., Damante, G., et al. (2008). Subfunctionalization of duplicated zebrafish pax6 genes by cis-regulatory divergence. *PLoS Genetics, 4*(2), e29.

Kumar, J. P., & Moses, K. (2001). Eye specification in Drosophila: Perspectives and implications. *Seminars in Cell & Developmental Biology, 12*(6), 469–474.

Kwan, K. M., Otsuna, H., Kidokoro, H., Carney, K. R., Saijoh, Y., & Chien, C. B. (2012). A complex choreography of cell movements shapes the vertebrate eye. *Development, 139*(2), 359–372.

Lagutin, O., Zhu, C. C., Furuta, Y., Rowitch, D. H., McMahon, A. P., & Oliver, G. (2001). *Six3* promotes the formation of ectopic optic vesicle-like structures in mouse embryos. *Developmental Dynamics, 221*, 342–349.

Lagutin, O. V., Zhu, C. C., Kobayashi, D., Topczewski, J., Shimamura, K., Puelles, L., et al. (2003). Six3 repression of Wnt signaling in the anterior neuroectoderm is essential for vertebrate forebrain development. *Genes & Development, 17*, 368–379.

Lane, B. M., & Lister, J. A. (2012). Otx but not Mitf transcription factors are required for zebrafish retinal pigment epithelium development. *PLoS ONE, 7*(11), e49357.

Lee, J., Willer, J. R., Willer, G. B., Smith, K., Gregg, R. G., & Gross, J. M. (2008). Zebrafish blowout provides genetic evidence for Patched1-mediated negative regulation of Hedgehog signaling within the proximal optic vesicle of the vertebrate eye. *Developmental Biology, 319*(1), 10–22.

Li, X., Perissi, V., Liu, F., Rose, D. W., & Rosenfeld, M. G. (2002). Tissue-specific regulation of retinal and pituitary precursor cell proliferation. *Science, 297*(5584), 1180–1183.

Li, Z., Joseph, N. M., & Easter, S. S. J. (2000). The morphogenesis of the zebrafish eye, including a fate map of the optic vesicle. *Developmental Dynamics, 218*, 175–188.

Liu, I. S., Chen, J. D., Ploder, L., Vidgen, D., van der Kooy, D., Kalnins, V. I., et al. (1994). Developmental expression of a novel murine homeobox gene (Chx10): Evidence for roles in determination of the neuroretina and inner nuclear layer. *Neuron, 13*(2), 377–393.

Liu, W., Lagutin, O., Swindell, E., Jamrich, M., & Oliver, G. (2010). Neuroretina specification in mouse embryos requires Six3-mediated suppression of Wnt8b in the anterior neural plate. *The Journal of Clinical Investigation, 120*(10), 3568–3577.

Loosli, F., Staub, W., Finger-Baier, K., Ober, E., Verkade, H., Wittbrodt, J., et al. (2003). Loss of eyes in zebrafish caused by mutation of chokh/rx3. *EMBO Reports, 4*, 894–899.

Loosli, F., Winkler, S., Burgtorf, C., Wurmbach, E., Ansorge, W., Henrich, T., et al. (2001). Medaka *eyeless* is the key factor linking retinal determination and eye growth. *Development, 128*, 4035–4044.

Loosli, F., Winkler, S., & Wittbrodt, J. (1999). Six3 overexpression initiates the formation of ectopic retina. *Genes & Development, 13*(6), 649–654.

Lopashov, G. V., & Stroeva, O. G. (1964). *Development of the eye; experimental studies.* Jerusalem: Israel Program for Scientific Translation.

Lupo, G., Liu, Y., Qiu, R., Chandraratna, R. A., Barsacchi, G., He, R. Q., et al. (2005). Dorsoventral patterning of the Xenopus eye: A collaboration of Retinoid, Hedgehog and FGF receptor signaling. *Development, 132*(7), 1737–1748.

Macdonald, R., Barth, K. A., Xu, Q., Holder, N., Mikkola, I., & Wilson, S. W. (1995). Midline signalling is required for Pax gene regulation and patterning of the eyes. *Development, 121* (10), 3267–3278.

Macdonald, R., Scholes, J., Strahle, U., Brennan, C., Holder, N., Brand, M., et al. (1997). The Pax protein Noi is required for commissural axon pathway formation in the rostral forebrain. *Development, 124*(12), 2397–2408.

Martinez-Morales, J. R., Dolez, V., Rodrigo, I., Zaccarini, R., Leconte, L., Bovolenta, P., et al. (2003). OTX2 activates the molecular network underlying retina pigment epithelium differentiation. *Journal of Biological Chemistry, 278*(24), 21721–21731.

Martinez-Morales, J. R., Rembold, M., Greger, K., Simpson, J. C., Brown, K. E., Quiring, R., et al. (2009). ojoplano-mediated basal constriction is essential for optic cup morphogenesis. *Development, 136*(13), 2165–2175.

Martinez-Morales, J. R., Rodrigo, I., & Bovolenta, P. (2004). Eye development: A view from the retina pigmented epithelium. *BioEssays, 26*(7), 766–777.

Martinez-Morales, J. R., Signore, M., Acampora, D., Simeone, A., & Bovolenta, P. (2001). Otx genes are required for tissue specification in the developing eye. *Development, 128*(11), 2019–2030.

Martinez-Morales, J. R., & Wittbrodt, J. (2009). Shaping the vertebrate eye. *Current Opinion in Genetics & Development, 19*(5), 511–517.

Mathers, P. H., Grinberg, A., Mahon, K. A., & Jamrich, M. (1997). The Rx homeobox gene is essential for vertebrate eye development. *Nature, 387*(6633), 603–607.

Matsuo, I., Kuratani, S., Kimura, C., Takeda, N., & Aizawa, S. (1995). Mouse Otx2 functions in the formation and patterning of rostral head. *Genes & Development, 9*(21), 2646–2658.

Medina-Martinez, O., Amaya-Manzanares, F., Liu, C., Mendoza, M., Shah, R., Zhang, L., et al. (2009). Cell-autonomous requirement for rx function in the mammalian retina and posterior pituitary. *PLoS ONE, 4*(2), e4513.

Mochii, M., Ono, T., Matsubara, Y., & Eguchi, G. (1998). Spontaneous transdifferentiation of quail pigmented epithelial cell is accompanied by a mutation in the Mitf gene. *Developmental Biology, 196*(2), 145–159.

Mui, S. H., Kim, J. W., Lemke, G., & Bertuzzi, S. (2005). Vax genes ventralize the embryonic eye. *Genes & Development, 19*(10), 1249–1259.

Muller, F., Rohrer, H., & Vogel-Hopker, A. (2007). Bone morphogenetic proteins specify the retinal pigment epithelium in the chick embryo. *Development, 134*(19), 3483–3493.

Nakayama, A., Nguyen, M. T., Chen, C. C., Opdecamp, K., Hodgkinson, C. A., & Arnheiter, H. (1998). Mutations in microphthalmia, the mouse homolog of the human deafness gene MITF, affect neuroepithelial and neural crest-derived melanocytes differently. *Mechanisms of Development, 70*(1–2), 155–166.

Nakayama, T., Fish, M. B., Fisher, M., Oomen-Hajagos, J., Thomsen, G. H., & Grainger, R. M. (2013). Simple and efficient CRISPR/Cas9-mediated targeted mutagenesis in Xenopus tropicalis. *Genesis, 51*(12), 835–843.

Nguyen, M. T., & Arnheiter, H. (2000). Signaling and transcriptional regulation in early mammalian eye development: A link between FGF and MITF. *Development, 127*, 3581–3591.

Peters, M. A. (2002). Patterning the neural retina. *Current Opinion in Neurobiology, 12*(1), 43–48.

Phillips, M. J., Perez, E. T., Martin, J. M., Reshel, S. T., Wallace, K. A., Capowski, E. E., et al. (2014). Modeling human retinal development with patient-specific induced pluripotent stem cells reveals multiple roles for visual system homeobox 2. *Stem Cells, 32*(6), 1480–1492.

Picker, A., Cavodeassi, F., Machate, A., Bernauer, S., Hans, S., Abe, G., et al. (2009). Dynamic coupling of pattern formation and morphogenesis in the developing vertebrate retina. *PLoS Biology, 7*(10), e1000214.

Pittack, C., Grunwald, G. B., & Reh, T. A. (1997). Fibroblast growth factors are necessary for neural retina but not pigmented epithelium differentiation in chick embryos. *Development, 124*(4), 805–816.

Pittack, C., Jones, M., & Reh, T. A. (1991). Basic fibroblast growth factor induces retinal pigment epithelium to generate neural retina in vitro. *Development, 113*, 577–588.

Planque, N., Turque, N., Opdecamp, K., Bailly, M., Martin, P., & Saule, S. (1999). Expression of the microphthalmia-associated basic helix-loop-helix leucine zipper transcription factor Mi in avian neuroretina cells induces a pigmented phenotype. *Cell Growth & Differentiation, 10*(7), 525–536.

Porges, Y., Gershoni-Baruch, R., Leibu, R., Goldscher, D., Zonis, S., Shapira, I., et al. (1992). Hereditary microphthalmia with colobomatous cyst. *American Journal of Ophthalmology, 114*(1), 30–34.

Porter, F. D., Drago, J., Xu, Y., Cheema, S. S., Wassif, C., Huang, S. P., et al. (1997). Lhx2, a LIM homeobox gene, is required for eye, forebrain, and definitive erythrocyte development. *Development, 124*(15), 2935–2944.

Raymond, S. M., & Jackson, I. J. (1995). The retinal pigmented epithelium is required for development and maintenance of the mouse neural retina. *Current Biology, 5*(11), 1286–1295.

Rebagliati, M. R., Toyama, R., Haffter, P., & Dawid, I. B. (1998). Cyclops encodes a nodal-related factor involved in midline signaling. *Proceedings of the National Academy of Sciences, 95*(17), 9932–9937.

Rembold, M., Loosli, F., Adams, R. J., & Wittbrodt, J. (2006). Individual cell migration serves as the driving force for optic vesicle evagination. *Science, 313*(5790), 1130–1134.

Rohr, K. B., Barth, K. A., Varga, Z. M., & Wilson, S. W. (2001). The nodal pathway acts upstream of hedgehog signaling to specify ventral telencephalic identity. *Neuron, 29*(2), 341–351.

Rowan, S., & Cepko, C. L. (2004). Genetic analysis of the homeodomain transcription factor Chx10 in the retina using a novel multifunctional BAC transgenic mouse reporter. *Developmental Biology, 271*(2), 388–402.

Sampath, K., Rubinstein, A. L., Cheng, A. M., Liang, J. O., Fekany, K., Solnica-Krezel, L., et al. (1998). Induction of the zebrafish ventral brain and floorplate requires cyclops/nodal signalling. *Nature, 395*(6698), 185–189.

Samuel, A., Housset, M., Fant, B., & Lamonerie, T. (2014). Otx2 ChIP-seq reveals unique and redundant functions in the mature mouse retina. *PLoS ONE, 9*(2), e89110.

Schwarz, M., Cecconi, F., Bernier, G., Andrejewski, N., Kammandel, B., Wagner, M., et al. (2000). Spatial specification of mammalian eye territories by reciprocal transcriptional repression of Pax2 and Pax6. *Development, 127*(20), 4325–4334.

Seth, A., Culverwell, J., Walkowicz, M., Toro, S., Rick, J. M., Neuhauss, S. C., et al. (2006). belladonna/(Ihx2) is required for neural patterning and midline axon guidance in the zebrafish forebrain. *Development, 133*(4), 725–735.

Sinn, R., & Wittbrodt, J. (2013). An eye on eye development. *Mechanisms of Development, 130*(6–8), 347–358.

Steinfeld, J., Steinfeld, I., Coronato, N., Hampel, M. L., Layer, P. G., Araki, M., et al. (2013). RPE specification in the chick is mediated by surface ectoderm-derived BMP and Wnt signalling. *Development, 140*(24), 4959–4969.

Steingrimsson, E., Copeland, N. G., & Jenkins, N. A. (2004). Melanocytes and the microphthalmia transcription factor network. *Annual Review of Genetics, 38*, 365–411.

Strauss, O. (2005). The retinal pigment epithelium in visual function. *Physiological Reviews, 85*(3), 845–881.

Suzuki, K. T., Isoyama, Y., Kashiwagi, K., Sakuma, T., Ochiai, H., Sakamoto, N., et al. (2013). High efficiency TALENs enable F0 functional analysis by targeted gene disruption in Xenopus laevis embryos. *Biology Open, 2*(5), 448–452.

Svoboda, K. K., & O'Shea, K. S. (1987). An analysis of cell shape and the neuroepithelial basal lamina during optic vesicle formation in the mouse embryo. *Development, 100*(2), 185–200.

Take-uchi, M., Clarke, J. D., & Wilson, S. W. (2003). Hedgehog signalling maintains the optic stalk-retinal interface through the regulation of Vax gene activity. *Development, 130*(5), 955–968.

Tena, J. J., Gonzalez-Aguilera, C., Fernandez-Minan, A., Vazquez-Marin, J., Parra-Acero, H., Cross, J. W., et al. (2014). Comparative epigenomics in distantly related teleost species identifies conserved cis-regulatory nodes active during the vertebrate phylotypic period. *Genome Research.*

Tetreault, N., Champagne, M. P., & Bernier, G. (2009). The LIM homeobox transcription factor Lhx2 is required to specify the retina field and synergistically cooperates with Pax6 for Six6 trans-activation. *Developmental Biology, 327*(2), 541–550.

Torres, M., Gómez-Pardo, E., & Gruss, P. (1996). *Pax2* contributes to inner ear patterning and optic nerve trajectory. *Development, 122*, 3381–3391.

Treisman, J. E. (1999). A conserved blueprint for the eye? *BioEssays, 21*(10), 843–850.

Turque, N., Denhez, F., Martin, P., Planque, N., Bailly, M., Begue, A., et al. (1996). Characterization of a new melanocyte-specific gene (QNR-71) expressed in v-myc-transformed quail neuroretina. *EMBO Journal, 15*(13), 3338–3350.

Viczian, A. S., Solessio, E. C., Lyou, Y., & Zuber, M. E. (2009). Generation of functional eyes from pluripotent cells. *PLoS Biology, 7*(8), e1000174.

Vogel-Hopker, A., Momose, T., Rohrer, H., Yasuda, K., Ishihara, L., & Rapaport, D. H. (2000). Multiple functions of fibroblast growth factor-8 (FGF-8) in chick eye development. *Mechanisms of Development, 94*(1–2), 25–36.

Wagner, G. P. (2007). The developmental genetics of homology. *Nature Reviews Genetics, 8*(6), 473–479.

Wallis, D. E., Roessler, E., Hehr, U., Nanni, L., Wiltshire, T., Richieri-Costa, A., et al. (1999). Mutations in the homeodomain of the human SIX3 gene cause holoprosencephaly. *Nature Genetics, 22*(2), 196–198.

Westenskow, P., Piccolo, S., & Fuhrmann, S. (2009). Beta-catenin controls differentiation of the retinal pigment epithelium in the mouse optic cup by regulating Mitf and Otx2 expression. *Development, 136*(15), 2505–2510.

Wilson, S. W., & Houart, C. (2004). Early steps in the development of the forebrain. *Developmental Cell, 6*(2), 167–181.

Yasuoka, Y., Suzuki, Y., Takahashi, S., Someya, H., Sudou, N., Haramoto, Y., et al. (2014). Occupancy of tissue-specific cis-regulatory modules by Otx2 and TLE/Groucho for embryonic head specification. *Nature Communications, 5*, 4322.

Yin, J., Morrissey, M. E., Shine, L., Kennedy, C., Higgins, D. G., & Kennedy, B. N. (2014). Genes and signaling networks regulated during zebrafish optic vesicle morphogenesis. *BMC Genomics, 15*, 825.

Zhang, L., Mathers, P. H., & Jamrich, M. (2000). Function of Rx, but not Pax6, is essential for the formation of retinal progenitor cells in mice. *Genesis, 28*(3–4), 135–142.

Zhao, S., Hung, F. C., Colvin, J. S., White, A., Dai, W., Lovicu, F. J., et al. (2001). Patterning the optic neuroepithelium by FGF signaling and Ras activation. *Development, 128*(24), 5051–5060.

Zou, C., & Levine, E. M. (2012). Vsx2 controls eye organogenesis and retinal progenitor identity via homeodomain and non-homeodomain residues required for high affinity DNA binding. *PLoS Genetics, 8*(9), e1002924.

Zuber, M. E., Gestri, G., Viczian, A. S., Barsacchi, G., & Harris, W. A. (2003). Specification of the vertebrate eye by a network of eye field transcription factors. *Development, 130*(21), 5155–5167.

Zuber, M. E., Perron, M., Philpott, A., Bang, A., & Harris, W. A. (1999). Giant eyes in Xenopus laevis by overexpression of XOptx2. *Cell, 98*(3), 341–352.