Human Genetics (2019) 138:973–991
https://doi.org/10.1007/s00439-018-1948-2

REVIEW

Human eye conditions: insights from the fly eye

Pedro Gaspar[1] · Isabel Almudi[2] · Maria D. S. Nunes[1] · Alistair P. McGregor[1]

Received: 5 February 2018 / Accepted: 20 October 2018 / Published online: 1 November 2018

Abstract
The fruit fly *Drosophila melanogaster* has served as an excellent model to study and understand the genetics of many human diseases from cancer to neurodegeneration. Studying the regulation of growth, determination and differentiation of the compound eyes of this fly, in particular, have provided key insights into a wide range of diseases. Here we review the regulation of the development of fly eyes in light of shared aspects with human eye development. We also show how understanding conserved regulatory pathways in eye development together with the application of tools for genetic screening and functional analyses makes *Drosophila* a powerful model to diagnose and characterize the genetics underlying many human eye conditions, such as aniridia and retinitis pigmentosa. This further emphasizes the importance and vast potential of basic research to underpin applied research including identifying and treating the genetic basis of human diseases.

Introduction

The sequencing of the genome of the fruit fly *Drosophila melanogaster* in 2000 (Adams et al. 2000; Myers et al. 2000; Rubin and Lewis 2000) and subsequent comparative genomic studies showed that approximately 70% of human disease-associated genes have a single *Drosophila* homolog (e.g. Reiter et al. 2001; Yamamoto et al. 2014). This highlights the relevance of this model organism to study the function of conserved genes and their roles in human disease (Wangler et al. 2015). Indeed, studies of the genetic regulation of *Drosophila* development over the last 30 years have provided many crucial insights into the genetic basis and progression of a wide range of human conditions from cancer to neurodegeneration and aging (Burke et al. 2017; Kreipke et al. 2017; Michno et al. 2005; Sen and Cox 2017; Sonoshita and Cagan 2017).

The compound eye of *Drosophila* in particular has proven to be an excellent model for many diseases despite the noticeable anatomical differences between insect and vertebrate eyes (Fig. 1; Table 1). The *Drosophila* eye consists of a regular array of several 100 individual light-sensing hexagonal structures called ommatidia (Cagan 2009; Hilbrant et al. 2014; Kumar 2012, 2018; Posnien et al. 2012), which together project a single image to the brain (Land 2005) (Fig. 1). The human "camera" eye also projects one image but from a single lens (Fig. 1). Although humans have a much narrower field-of-view than fruit flies, our eyes achieve higher spatial resolution and acuity (Borst 2009) because of thousands of sensory cells (rods and cones) packed tightly into the retina (Jonas et al. 1992), while each *Drosophila* ommatidia only has eight photoreceptors and 11 accessory cells (Treisman 2013) (Fig. 1). At the basic structural level, however, both insect and vertebrate eyes are made up of a lens to focus light, a neural retina with photoreceptors to sense the light and a pigmented epithelium to protect photoreceptor signaling from scattered or diffracted light (Charlton-Perkins et al. 2011; Sanes and Zipursky 2010) (Fig. 1). Moreover, decades of research have revealed that the development of *Drosophila* eyes is regulated by genetic pathways that are conserved between flies and humans, and consequently studies of *Drosophila* have taught us much about human eyes (Gehring 2005; Halder et al. 1995; Kumar and Moses 2001; Vopalensky and Kozmik 2009; Wawersik and Maas 2000).

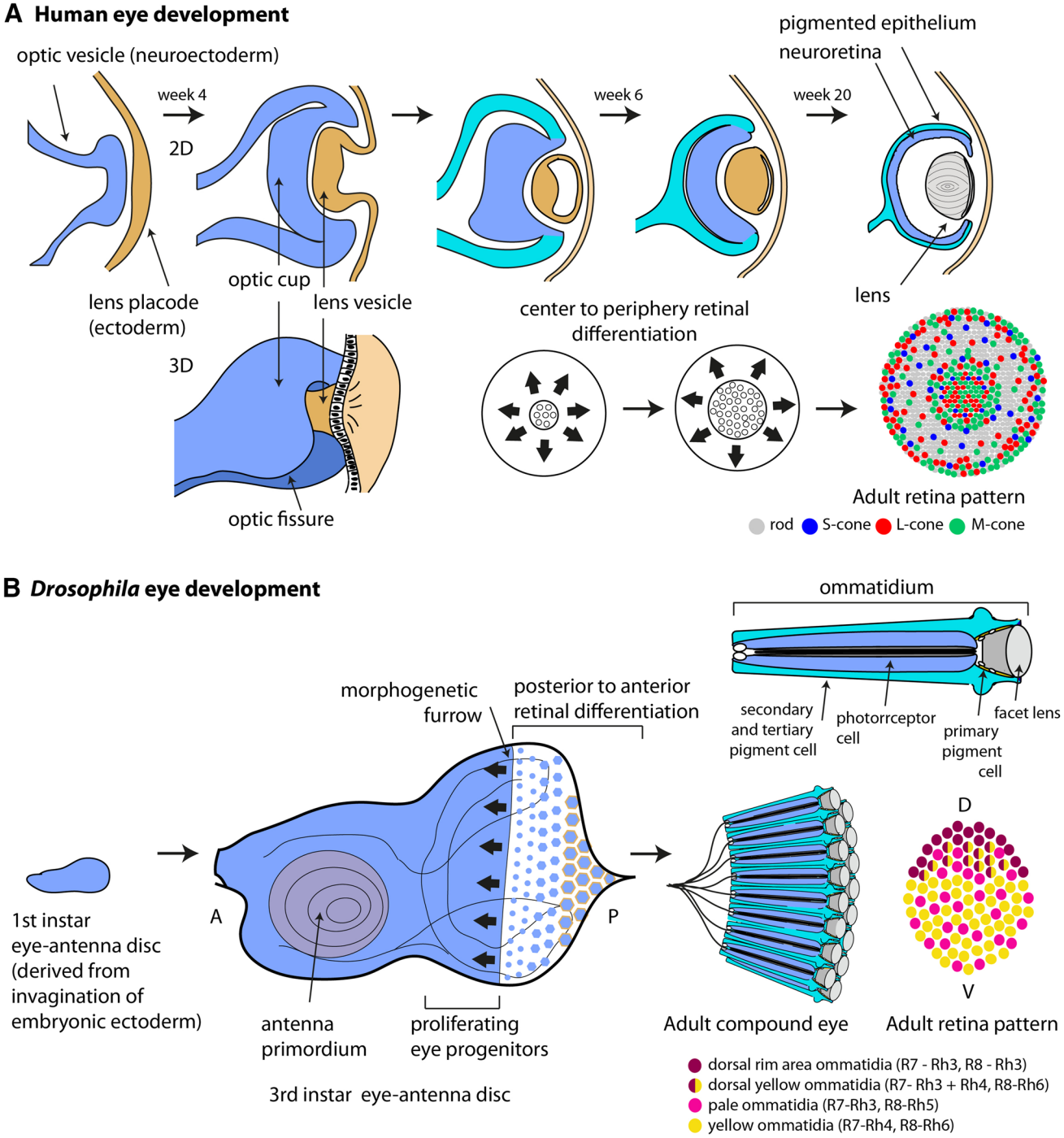
In this review, we focus on how research on the genetic regulation of *Drosophila* eye development has informed our understanding of human eye development and highlight the

Pedro Gaspar and Isabel Almudi contributed equally.

✉ Alistair P. McGregor
amcgregor@brookes.ac.uk

[1] Department of Biological and Medical Sciences, Oxford Brookes University, Gipsy Lane, Oxford OX3 0BP, UK

[2] Centro Andaluz de Biología del Desarrollo, CSIC/ Universidad Pablo de Olavide, Carretera de Utrera Km1, 41013 Sevilla, Spain



power and potential of research on fly eyes to better understand and potentially treat human conditions (Table 1).

Eye development

Selector genes of invertebrate and vertebrate eye development

The *Drosophila* eyes develop from evagination of the embryonic neuroectoderm to form two epithelial sacs, the so-called eye-antennal imaginal discs (Casares and

◂**Fig. 1** Comparative overview of human and *Drosophila* eye development. Eye development from week 4 to week 20 of human embryogenesis **a**. At week 4 of development, the optic vesicles evaginate from the forebrain neuroectoderm inducing the adjacent ectoderm to form the lens placode. Between weeks 4 and 6, the optic vesicle invaginates on itself, forming the optic cup, which partially encapsulates the invaginating lens vesicle (interrupted posteriorly by the optic fissure). After week 6 and until week 20, the optic cup differentiates into two main layers, the neuroretina and the pigmented epithelium, while the lens vesicle thickens and forms the crystalline lens. The neural cells in the neuroretina differentiate from the center to the periphery of the optic disc, such that the adult retina pattern is set with circumferential bands or zones enriched in specific photoreceptors. Eye development and adult retina patterning of *Drosophila* **b**. The eye imaginal disc develops from an invagination of the embryonic ectoderm, being subdivided early to form precursor regions to the eye and antenna (1st larval instar imaginal disc). During the 3rd larval instar, differentiation of ommatidia into clusters of 8 photoreceptor cells progresses from the posterior to the anterior of the disc, as a band of apical cell constrictions termed the morphogenetic furrow sweeps across the tissue. The longitudinal structure of the adult ommatidium shows an apical facet lens lined basally by primary pigment cells and focusing into a central rhabdomere projected by the lateral membrane of the photoreceptor cells. The cluster of photoreceptor cells is surrounded by secondary and tertiary pigment cells. The adult retina is patterned dorso-ventrally into two main zones, a dorsal third consisting of the dorsal rim area and dorsal yellow ommatidia, and a ventral area with a stochastic pattern of yellow and pale ommatidia. Ommatidia in these areas have a specific repertoire of rhodopsin (Rh) gene expression in photoreceptors R7 and R8 (A—anterior, P—posterior, D—dorsal, V—ventral, R—photoreceptor, Rh—rhodopsin)

Almudi 2016; Green et al. 1993; Younossi-Hartenstein et al. 1993) (Figs. 1, 2). This region is characterized by the early expression of several conserved transcription factors, Orthodenticle (Otd)/Otx and the Pax6 homologues Twin of eyeless (Toy) and Eyeless (Ey) in the posterior region of the epithelial sac, which will give rise to the eye, ocelli, and head capsule, and Cut in the anterior region, which will mostly give rise to the antenna and maxillary palps (Czerny et al. 1999; Kenyon et al. 2003) (Fig. 2).

Much like in *Drosophila*, vertebrate eye development is centered on the activity of core selector genes, namely the *Pax6* gene. Vertebrate *Pax6* genes encode two alternatively spliced variants that differ in the presence of exon 5a. In contrast, *Drosophila Pax6* and *Pax6(5a)* homologues arose as separate loci from a relatively recent gene duplication event (Aldaz et al. 2003; Jun et al. 1998). Like in vertebrates, the two *Drosophila Pax6* genes, *ey* and *toy* (Czerny et al. 1999; Quiring et al. 1994), and two *Pax6(5a)* genes, *eyegone* (*eyg*) and *twin-of-eyegone* (*toe*) (Jang et al. 2003; Jun et al. 1998) have distinct roles in eye development. *ey* and *toy* promote primarily retinal specification, whereas *eyg* mainly promotes cell proliferation (Chao 2004; Dominguez et al. 2004). Each *Pax6*/*Pax6*(*5a*) orthologue also acts through distinct transcriptional mechanisms, with Ey acting as a transcriptional activator, while Eyg seems to act as a transcriptional repressor (Chao 2004; Dominguez et al. 2004; Punzo 2004; Punzo et al. 2001; Yao and Sun 2005).

Based on its sufficiency for eye development in *Drosophila* and vertebrates, it was originally proposed that *Pax6* functions at the highest level of a hierarchy of genes whose sequential expression leads to eye development (Gehring 1996). Indeed, three core members of this postulated hierarchy: *eyes absent* (*eya*) (EYA1, EYA2, EYA3), *sine oculis* (*so*, SIX1, SIX2 and SIX3), and *dac* (DACH1) have been identified in *Drosophila* and vertebrates, and share similar temporal expression patterns during eye development (Bonini et al. 1997; Chen et al. 1997; Pignoni et al. 1997; Shen and Mardon 1997; Treisman 1999; Zuber 2003). However, rather than acting in a simple linear pathway, it seems that positive transcriptional feedback organizes these core selector genes into an interconnected network (Desplan 1997). This regulatory structure appears critical to induce retinal tissue as evidenced by mis-expression experiments where core genes fail to induce ectopic eyes if any of the other critical factors is absent (Bonini et al. 1997). Positive transcriptional feedback is also needed for these genes to activate a second, independently regulated phase of gene expression, as many of these genes function at several stages of eye development. For instance, *ey, eya* and *so* are critical for growth of the eye primordium and initiation of differentiation (Bonini et al. 1993; Cheyette et al. 1994; Halder et al. 1998; Jang et al. 2003; Mardon et al. 1994; Pignoni et al. 1997), while *eya* and *so* are then also required for progression of photoreceptor differentiation (Pignoni et al. 1997), and *ey* is needed for rhodopsin gene expression (Papatsenko et al. 2001; Sheng et al. 1997).

Cellular differentiation

During the first larval stages of *Drosophila*, the epithelial cells are undifferentiated progenitor cells that proliferate continuously due to the combined activity of the genes *ey, homothorax* (*hth*), *toy, teashirt (tsh), tiptop* and *yorkie (yki)* (Figs. 1, 2) (Bessa et al. 2009; Bessa and Casares 2005; Datta et al. 2009; Laugier et al. 2005). The growth of the *Drosophila* eye is interconnected with the organization of both antero-posterior and dorso-ventral axes during development, such as established through the action of Wingless (Wg) and Notch (N) (Dominguez and de Celis 1998; Heberlein et al. 1998; Papayannopoulos et al. 1998). In particular, N induces proliferation by activating the expression of *eyg* (Dominguez et al. 2004). At the same time, the first wave of retinal determinants, mainly *ey* and *toy*, induce and reinforce the expression of other retinal determinants, *eya, so* and *dachshund* (*dac*) (Fig. 2) (reviewed in Casares and Almudi 2016; Davis and Rebay 2017).

The differentiation of the cells that form the ommatidia in *Drosophila* is a sequential process. A morphogenetic

Table 1 Genes that cause human eye conditions and their *Drosophila* orthologs

Human gene	Phenotype	References	*Drosophila* gene	Phenotype	References
PAX6	Aniridia, anophthalmia, microphthalmia	Glaser et al. (1992); Jordan et al. (1992); Ton et al. (1991)	*eyeless*	Reduced eyes	Patterson and Muller (1930)
EYA1	Congenital cataracts; anterior segment anomalies	Azuma et al. (2000)	*eyes absent*	Eye facets completely absent in strong alleles	Bonini et al. (1993)
SIX1	Catarats; branchio-oto-renal syndrome; deafness	(Salam et al. 2000)	*sine oculis*	Eyes reduced to small groups of ommatidia, occasionally missing	Cheyette et al. (1994)
SIX5	Branchio-oto-renal syndrome; deafness	Hoskins et al. (2007)			
SIX3	Holoprosencephaly and microphthalmia	Wallis et al. (1999)	*optix*	Eye defects	Weasner et al. (2007)
SIX6	Optic disc anomalies with retinal and/or macular dystrophy	Aldahmesh et al. (2013); Yariz et al. (2015)			
DACH1	Microphthalmia, anophthalmia, and coloboma	Warburg (1993)	*dachshund*	Severely reduced or no eyes	Shen and Mardon (1997)
MEIS2	Cleft palate; cardiac defects; mental retardation	Crowley et al. (2010)	*homothorax*	Overgrowths of eye tissue; loss of ventral and dorsal head structures	Pichaud and Casares (2000)
ATOH7	Congenital blindness; nystagmus; shallow anterior chamber; massive retrolental mass; retinal nonattachment	Ghiasvand et al. (2011)	*atonal*	Neuroanatomy defective; adult photoreceptors missing	Jarman et al. (1995)
OTX2	Microphthalmia, syndromic 5; retinal dystrophy; early onset, with or without pituitary dysfunction; cone–rod retinal dystrophy-2	Freund et al. (1997); Ragge et al. (2005)	*oc*	Eyes somewhat reduced and body size dwarfed. Phototaxis normal	Benzer (1967)
CRX	Cone–rod dystrophy; retinitis pigmentosa; LCA	Freund et al. (1997); Freund et al. (1998); Sohocki et al. (1998)			
CRB1	Pigmented paravenous chorioretinal atrophy; retinitis pigmentosa-12, autosomal recessive	den Hollander et al. (1999)	*Crumbs*	Mild overgrowth of adult eyes	Ling et al. (2010)
EYS	Retinitis pigmentosa 25	Abd El-Aziz et al. (2008)	*Eyes Shut*	Rhabdomere defects	Zelhof et al. (2006)
PAX2	Optic nerve coloboma	Favor et al. (1996); Sanyanusin et al. (1995)	*D-Pax2*	Eyes small, rough, and glazed	Fu et al. (1998)
SHH	Holoprosencephally	Roessler et al. (1996)	*hedgehog*	Eye small and narrow with about 150 facets	Heberlein et al. (1995); Lee et al. (1992); Renfranz and Benzer (1989)
RHO	Autosomal dominant retinitis pigmentosa	Bhattacharya et al. (1991); Dryja et al. (1991); Dryja et al. (1990)	ninaE	Rhabdomeres 1–6 is smaller than normal; light-independent degeneration of R1-6 rhabdomeres	Colley et al. (1995); Kurada and O'Tousa (1995)
PROMININ-1	Autosomal recessive retinal degeneration	Maw et al. (2000)	*Prominin*	Defective photoreceptor morphogenesis; disrupted inter-rhabdomeral space	Zelhof et al. (2006)

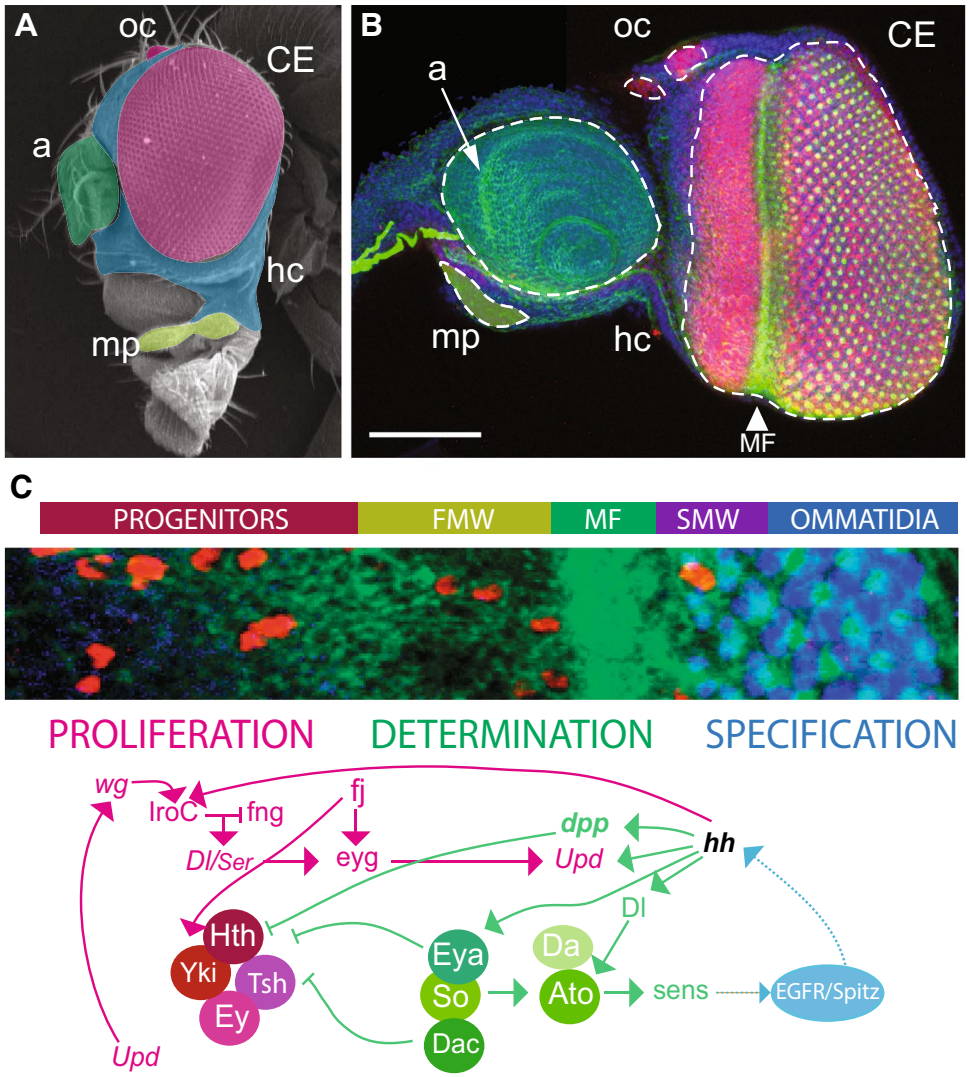


Fig. 2 *Drosophila melanogaster* eye determination and gene regulatory network. *Drosophila* adult head **a** and eye-antennal imaginal disc stained with anti-Eya (magenta), DAPI (blue) and phalloidin-AlexaFluor488 (Green) **b**. Color code represents the larval structures that will give rise to the structures of the adult head: compound eye (CE, magenta), ocelli (oc, dark magenta), antenna (a, dark green), maxillary palp (mp, light green), and head capsule (hc, blue). **c** Section of an eye imaginal disc showing the compartments where proliferation (most anterior), determination (around MF) and specification (posterior to MF) are occurring. From anterior to posterior (left to right): progenitors are characterized by high levels of proliferation (mitotic cells in red), followed by synchronic cells at G1, the first mitotic wave (FMW), morphogenetic furrow (MF), and cells differentiating (second mitotic wave, SMW) into ommatidia most posteriorly. Mitotic cells are stained using an anti-PH3 antibody (red), MF is marked with Phalloidin-AlexaFluor488 (green) and photoreceptors are shown using anti-Elav, in blue. A simplified gene network showing the main molecules involved in the three processes is displayed. Color code highlights the process in which each molecule has its main role. Scale bar 50 µm. All the panels show anterior to the left and posterior to the right

wave, designated as the morphogenetic furrow (MF, Figs. 1, 2), sweeps across the epithelium from the most posterior region towards the anterior promoting the recruitment and differentiation of the different types of cells that constitute the ommatidium (reviewed in Kumar 2011; Lee and Treisman 2002). During differentiation, the activity of Hedgehog ahead of the MF triggers N-dependent activation of the proneural gene *atonal* (*ato*) and restriction of its expression to a single cell in each proneural cluster, the R8 cell, which differentiates into the first photoreceptor of the ommatidial cluster (Jarman et al. 1994, 1995) (Fig. 2). Similarly, in zebrafish, retinal neurogenesis has been shown to occur in a wave starting in the optic cup adjacent to the optic stalk and spreading outwards, and is dependent on expression of Sonic Hedgehog and the Ato homologue Ath5 (Masai et al. 2000; Neumann and Nuesslein-Volhard 2000). In primates, differentiation also follows sequential waves of gene expression, emanating from the center of the optic disc to

its periphery (Cornish et al. 2005; Hendrickson et al. 2008) (Fig. 1). Much like Ato in *Drosophila*, Ath5 in mice seems to be essential to specify the first retinal neurons, the retinal ganglion cells (Brzezinski et al. 2012; Sun et al. 2003). In a recent study, gene replacement of *Drosophila* Ato with the mouse ortholog Ath1 demonstrated its ability to recapitulate the correct specification of the initial photoreceptors in *Drosophila*, albeit with changes in the pattern of retinal differentiation (Weinberger et al. 2017). Furthermore, in zebrafish, the early differentiating red cones recruit undifferentiated cells to drive further cone cell differentiation, in a process analogous to R8 recruitment of other photoreceptors in *Drosophila* (Raymond and Barthel 2004). Therefore, the initial specification of photoreceptors from undifferentiated progenitor cells appears to have many similarities between flies and vertebrates (Fig. 1).

In flies, Ato activates the expression of *senseless* (*sens*), whereas in the two adjacent remaining cells, Rough inhibits *sens* to specify the R2 and R5 photoreceptors (Pepple et al. 2008). The rest of the photoreceptors are specified in a sequential manner, involving the activity of the epidermal growth factor receptor (EGFR) signaling pathway, much of which was first delineated in *Drosophila* by the analysis of mutants affecting photoreceptor differentiation (Freeman 1996, 1997; Kumar et al. 1998). During this specification process, photoreceptors are specialized by expression of specific color-detecting rhodopsins, a process that shares some similarities again between flies and vertebrates (Fig. 1).

In flies, the Otx-family transcription factor Otd regulates the transcriptional repressor Defective Proventriculus (Dve) to regulate rhodopsin gene expression in specific photoreceptor subtypes (Johnston et al. 2011; Yan et al. 2017). In mice, the genes *Nr2e3* and *Nrl* also act with Otx-family members, like Crx, the orthologue of fly Otd, to activate rod opsin expression and repress cone opsin expression (Cheng et al. 2004; Hennig et al. 2008; Kaewkhaw et al. 2015; Peng et al. 2005). Interestingly, like Otd, human OTX1 and OTX2 can induce *dve* expression in *Drosophila* photoreceptors, suggesting conserved mechanisms of OTX-mediated regulation of photoreceptor specification between flies and humans (Terrell et al. 2012). Differentiation of yellow and pale ommatidial subtypes in *Drosophila* is based on the stochastic expression of the PAS-bHLH transcription factor Spineless, which determines Rh3 expression, and is counteracted by Spalt-major (Sal) and Otd to select expression of Rh4 (Fig. 1) (Johnston et al. 2011; Tahayato et al. 2003; Wernet et al. 2006). Interestingly, in mice, Sall3 (homolog of *sal*) has been shown to activate opsins and in humans expression of red versus green opsins also relies on a stochastic mechanism (de Melo et al. 2011; Nathans et al. 1989; Wang et al. 1992). Although different to that of *Drosophila*, this stochastic mechanism may share aspects of counter-regulation by Sal and OTX factors.

Overall, current research suggests that late photoreceptor specification by regulation of rhodopsin gene expression shares many conserved mechanisms between flies and vertebrates, which highlights this as an important area of focus for understanding human retinal diseases using the *Drosophila* model.

Insights into human eye conditions from *Drosophila*

Research on *Drosophila Pax6* genes and their impact on understanding eye developmental diseases

As mentioned above, in both flies and humans, oculogenesis is the product of a conserved gene regulatory network centered on the activity of *Pax6* (Gehring 2014; Quiring et al. 1994). The *Drosophila Pax6* gene, *ey*, was cloned first and functionally analyzed, and then shown to share a high level of sequence conservation with the *Small eye* gene in mice and the *Aniridia* gene in humans, all now collectively established as *Pax6* functional homologues (Halder et al. 1995; Quiring et al. 1994). Nearly 300 dominant mutations in the human *Pax6* locus have been described and most of these mutations lead to iris hypoplasia or total loss of the iris associated with cataracts and corneal changes, a condition designated as aniridia (Glaser et al. 1992; Hanson et al. 1994; Jordan et al. 1992; Verbakel et al. 2018). Other mutations in *Pax6* (and other functionally conserved genes in eye development) can also cause failed embryonic optic fissure closure in MAC (microphthalmia–anophthalmia–coloboma) spectrum diseases, like anophthalmia, characterized by absence of one or both eyes; microphthalmia, characterized by abnormally small eyes with various malformations, and colobomas, characterized by an opening in the iris, retina, choroid or optic disc (Glaser et al. 1994; Skalicky et al. 2013; Williamson and FitzPatrick 2014). Of the core eye regulators, apart from *Pax6*, mutations in *Six5*, for example, have been shown promote cataract formation in mice (Klesert et al. 2000; Sarkar et al. 2000) and mutations in *EYA1* have been associated with congenital cataracts (Azuma et al. 2000).

Despite the differences in development of the optic primordium between *Drosophila* and vertebrates, Pax6/E*y* is necessary to induce eye formation, and ectopic expression of *ey* or mouse *Pax6* is sufficient to induce ectopic eyes (Halder et al. 1995). Additionally, a *Drosophila* eye enhancer of *ey* is capable of driving many features of endogenous *Pax6* expression in mice (Xu et al. 1999). These experiments have established the *Drosophila* model as suitable to study conserved *Pax6* functions in eye development and disease. It is, however, worth noting that based on the human and mice mutant phenotypes, *Pax6* in vertebrates seems more critical for lens development (Glaser et al. 1994).

The fly eye, which develops as an evagination of the embryonic ectoderm, much like the vertebrate lens vesicle, may thus bear greater similarities in genetic regulation to this structure than to the whole vertebrate eye (Charlton-Perkins et al. 2011) (Fig. 1). Of special mention in this respect is the highly conserved regulation of lens crystallin proteins by *Drosophila* Pax2 through the same binding sites as vertebrate Pax6 (Blanco et al. 2005; Kozmik et al. 2003). Lens crystallins are a family of ancient proteins, found even in jellyfish, where their expression in lentoid bodies relies on the activity of the ancestral PaxB transcription factor (Kozmik et al. 2003). Therefore, it appears that the *Pax2* gene may have been co-opted into lens development in *Drosophila*, whereas vertebrate *Pax6* has retained or reacquired that function. As such, *Drosophila* research into Pax2 regulation of *Crystallin* gene expression may prove essential to uncover mechanisms of vertebrate lens abnormalities in *Pax6* mutations.

Drosophila contributions to understanding conserved aspects of the gene regulatory logic of eye development

Drosophila research has been instrumental in understanding and modeling the gene regulatory logic underlying eye differentiation (Frankfort and Mardon 2002). Recently, this was again shown by rigorous spatiotemporal quantification and computational modeling that helped to reveal general principles about the logic of the Hedgehog, Notch and EGFR signals during eye growth and morphogenesis (Fried et al. 2016; Zhu et al. 2016). Indeed, the regulatory logic among genes involved in eye determination was shown to be very similar between flies and vertebrates. For example, switching off or dampening *ey*/*Pax6* expression is required for photoreceptor fate specification in both flies and vertebrates, as in both cases maintenance or prolonged high levels of Ey/Pax6 after eye determination have been associated with failures of neuronal differentiation (Belecky-Adams et al. 1997; Canto-Soler et al. 2008; Toy et al. 2002).To achieve this transition, the positive feedback loop that maintains anterior *ey* expression in eye precursors must be interrupted. In *Drosophila*, this inhibition results from rewiring the network such that Eya-So directly represses *ey* transcription in differentiating cells (Atkins et al. 2013). Interestingly, increasing the levels of Eya and So anterior to the MF reduces *ey* expression (Atkins et al. 2013). Dac appears to be crucial for this switching, as Dac is required for *ey* repression posterior to the MF and can cooperate with Eya and So to inhibit *ey* transcription in anterior cells (Atkins et al. 2013). One idea is that Dac joins Eya-So to switch the complex into a repressive activity (Davis and Rebay 2017). Although a direct repressive function has not been confirmed in *Drosophila*, this may be a conserved function of Dac, as mammalian DACH1 can recruit co-repressors and directly repress target gene transcription (Chen et al. 2013; Chu et al. 2014; Li et al. 2003; Sundaram et al. 2008; Wu et al. 2003, 2006, 2008, 2009, 2011; Zhao et al. 2015). On the other hand, mammalian Eya is thought to convert repressive SIX–DACH complexes to activating EYA–SIX–DACH complexes (Li et al. 2002, 2003).

A second example of regulatory switching is the coordination of proliferation with specification in retinal progenitors. Competency to switch from proliferation to specification is initiated when Ey activates transcription of *eya* and *so*, which in turn reinforces *ey* expression and promotes *dac* transcription (Fig. 1) (Anderson et al. 2006; Atkins et al. 2013; Bonini et al. 1997; Chen et al. 1997; Halder et al. 1998; Niimi et al. 1999; Ostrin 2006; Pappu 2005; Pignoni et al. 1997; Salzer and Kumar 2009). Dac then terminates the pro-proliferative role of Hth–Yki complexes by inhibiting Hth expression and interfering with the ability of Hth–Yki to activate transcription of the pro-growth *bantam* microRNA (Fig. 2) (Bras-Pereira et al. 2015). Subsequently, Ey cooperates with Eya–So to activate *ato* transcription, which specifies the first photoreceptor to initiate ommatidial assembly (Fig. 2) (Jemc and Rebay 2007; Zhang et al. 2006; Zhou et al. 2014). This results in a mutual inhibition between the Ey–Hth–Tsh and Ey–Eya–So–Dac signaling networks, which drives precursors from asynchronous proliferation to coordinated differentiation.

As in the first switching example, Dac appears to be a key player in the transcriptional repression events that drive developmental transition. How these transitions are orchestrated at the level of chromatin regulation and transcriptional regulation is poorly understood. One idea stemming from *Drosophila* studies is that core eye determination factors recruit Polycomb group proteins (PcG) to promote switching from proliferative precursors to differentiating retinal cells. Indeed, deletion of repressive Polycomb Group genes leads to ectopic Hth and Tsh expression posterior to the MF, which is reminiscent of *eya, so*, or *dac* loss (Janody et al. 2004). Another intriguing observation is that mutation of *skuld* or *kohtalo*, two Trithorax Group genes, leads to inappropriate maintenance of Ey posterior to the MF (Janody et al. 2004). Consistent with this, Eya1 and Six1 recruit the SWI/SNF complex to activate downstream target transcription that drives cochlear neurogenesis (Ahmed et al. 2012), while Dach1 primarily associates with co-repressors, as discussed above.

The rewiring mechanisms of the retinal determination gene network discussed above are now beginning to give a better picture of developmental transitions, such as the transition from proliferative precursors to differentiating retinal cells. These mechanisms, namely the role of DACH1 in cell proliferation, are also beginning to be appreciated in the context of human cancer (Chen et al. 2013; Chu et al. 2014; Wu et al. 2006, 2009, 2011), but further studies in vertebrate

models are needed to investigate how these mechanisms may be impaired specifically in eye developmental diseases.

Retinal degeneration models

As highlighted earlier in this review, the *Drosophila* compound eye has little resemblance to the human eye morphologically and yet the gene regulatory networks governing their development are remarkably similar. At a cellular level, the fly and human retinas share many similarities, namely in the structure of photoreceptors and in the genetic and molecular bases of phototransduction, both of which are frequently affected in retinal disease.

Since the mid-70s genetic screens have been designed in *Drosophila* to identify mutations where the morphogenesis of the eye is normal, but photoreceptor cells degenerate from the onset of adult visual function (Harris and Stark 1977; Harris et al. 1976; Hotta and Benzer 1970; Steele and O'Tousa 1990; Yoon et al. 2000). These studies revealed mutants that lead to either a light-independent (Bentrop 1998; Dolph et al. 1993; Lee et al. 1996; Raghu et al. 2000) or light-dependent photoreceptor degeneration (Meyertholen et al. 1987; Stark and Sapp 1987; Steele and O'Tousa 1990). This was of great relevance to understanding the mechanisms of many inherited degenerative diseases that cause blindness in humans, such as Retintis Pigmentosa, a disease that affects 1 in 4000 people, and is associated with progressive degeneration from night blindness to full blindness, or Leber congenital amaurosis (LCA), the most early and severe form of inherited retinal dystrophy, accounting for at least 5% of inherited retinal diseases (Verbakel et al. 2018). Animal models have shown that retinal degeneration in these cases results from cell death via apoptosis (Chang et al. 1993; Chen et al. 1999; Liu et al. 1999).

Mutations in humans that cause Retinitis Pigmentosa have been mapped to more than 80 known genes, and the genetics of their inheritance is complex, from autosomal dominant or recessive to X-linked (Ali et al. 2017; Daiger et al. 2007; Kaplan and Rozet 2008; Verbakel et al. 2018). Mutations in the human rhodopsin genes account for nearly 25% of the autosomal dominant retinitis pigmentosa (ADPR) cases (Alemaghtheh et al. 1993; Ali et al. 2017; Bhattacharya et al. 1991; Shokravi and Dryja 1993; Sung et al. 1993; Verbakel et al. 2018). Importantly, many of the mutations uncovered in *Drosophila* genetic screens affect the synthesis, maturation, intracellular transport, chemical recycling or degradation of the light-sensitive G protein-coupled receptor rhodopsins.

As in vertebrates, the phototransduction cascade in *Drosophila* is initiated by the photoactivation of a G protein-coupled receptor rhodopsin covalently linked to a chromophore, the carotenoid 3-hydroxyl, 11-*cis* retinal (Fig. 3). Light-stimulation induces isomerization of the chromophore thereby inducing a conformational change of rhodopsin to metarhodopsin that allows its interaction with a Gqα protein, thereby inducing multiple downstream processes, namely metabolism of diacylglycerol and the ensuing regulation of calcium influx (Fig. 3) (reviewed in Wang and Montell 2007; Xiong and Bellen 2013). Phototransduction is terminated upon metarhodopsin phosphorylation by GPRK1 and upon Arrestin2 binding, which lead to endocytic internalization (Fig. 3). Early studies in *Drosophila* revealed that mutations in genes involved in the termination of metarhodopsin activity, including *arr2, rdgB, rdgC, norpA* and *Camta*, cause light-dependent retinal degeneration (Fig. 3) (Wang and Montell 2007). In these cases, cell death is light dependent because it depends on the light-induced association of metarhodopsin with arrestin, the internalised accumulation of which triggers apoptosis in photoreceptors (Alloway et al. 2000; Kiselev et al. 2000; Kristaponyte et al. 2012). Similar to what happens in *Drosophila*, the vertebrate rhodopsin mutant RhK296E, common in autosomal dominant retinitis pigmentosa (ADPR), forms a stable complex with arrestin and accumulates in the inner segment of photoreceptors (Chen et al. 2006), suggesting this is a conserved mechanism in retinal degeneration between flies and vertebrates. Other *Drosophila* and vertebrate mutants highlight toxicity due to internalised accumulation of rhodopsin, such as in genes affecting endolysosomal degradation or the autophagy pathway (Chinchore et al. 2009; Hara et al. 2006; Komatsu et al. 2006; Xu et al. 2004). Furthermore, dominant mutations in *Drosophila* Rh1 were isolated that cause photoreceptor degeneration only in the heterozygous state (Colley et al. 1995; Kurada and O'Tousa 1995), with many being identical to those found in ADRP patients, implying that degeneration is dependent on the existence of both wild-type and mutant rhodopsin and revealing that dominant mutant rhodopsin interferes with the maturation of wild-type rhodopsin (Colley et al. 1995). Toxicity due to incorrect folding or maturation of rhodopsin has also been implicated by mutations in the *Drosophila* chaperones calnexin and Xport, which lead to Rh1 accumulation in the ER and reduced Rh1 levels in rhabdomeres and thereby cause light-enhanced retinal degeneration (Rosenbaum et al. 2006, 2011).

Uncontrolled activity of rhodopsin can also result in retinal degeneration. Indeed, this is the case in the *Drosophila* Rh1 PP100 mutant, where the mutant opsin persistently binds arrestin and there is a constitutive activity of the phototransduction cascade (Iakhine 2004). In this case, loss of either arrestin or the Gqα rescues the degenerative phenotype. This mechanism may be relevant to autosomal dominant congenital night blindness, where a mild retinal degeneration is seen as a result of constitutively active forms of rod opsin (Dryja 2000).

The transcriptional mechanisms regulating the expression of rhodopsin genes are yet another important factor

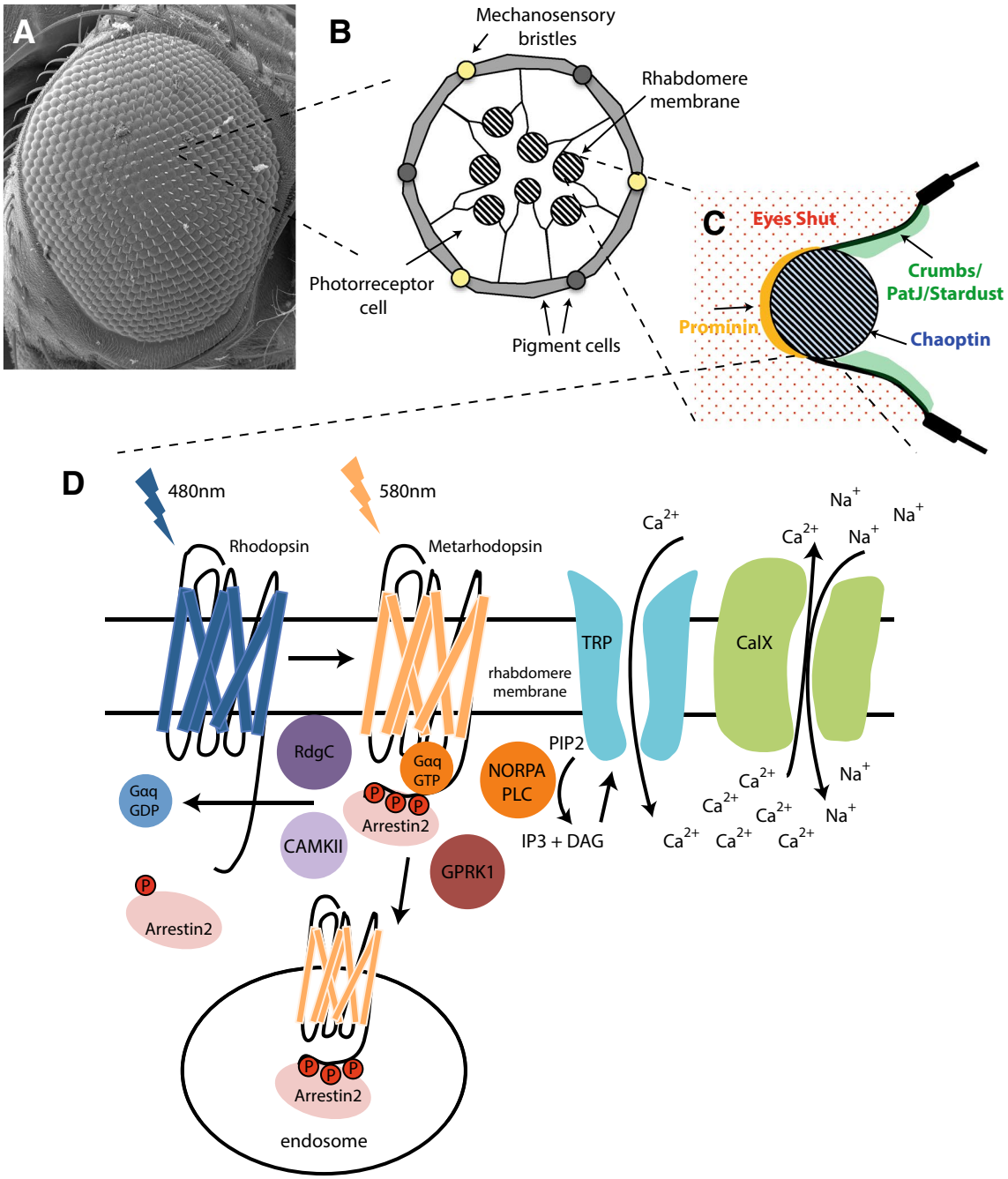


Fig. 3 The *Drosophila* phototransduction apparatus. The *Drosophila* compound eye **a** is composed of hundreds of ommatidia **b** each made up of a cluster of 8 photoreceptor cells surrounded by accessory cells. Each photoreceptor cell projects a microvilli dense membrane towards the center of the ommatidium, making up the light-sensitive rhabdomere **c**. The rhabdomere membrane is supported at its base by the Crumbs/PatJ/Stardust complex and at its core by the structural proteins Chaoptin, Prominin and Eyes Shut. Within the rhabdomere membrane **d**, the phototransduction cascade is initiated by the light-induced conformational change of rhodopsin into metarhodopsin, which in turn is able to become phosphorylated by GPRK1, interact with a Gαq protein and bind Arrestin2. This initiates a series of other reactions, from the conversion of PIP2 into IP3 and DAG to the internalization of metarhodopsin–arrestin complexes. DAG is able to stimulate Ca^{2+} influx via TRP channels, which in turn can be counterbalanced by Ca^{2+}/Na^{+} antiport by the CalX channel. Light-induced conformational change of metarhodopsin can promote its dephosphorylation by RdgC and phosphorylation of Arrestin2 by CAMKII, which promotes its dissociation, thus ensuing the recycling of rhodopsin's original state

commonly affected in retinal diseases. In *Drosophila*, the transcriptional activation of the Rh3 and Rh5 genes and transcriptional repression of Rh6 are orchestrated by the homeodomain protein Otd, and these functions can be partially complemented by the human Otd-related genes *OTX2* and *Crx*, both of which are expressed in human cones and rods and regulate many photoreceptor-specific genes (Terrell et al. 2012). Importantly, several homeodomain mutations in CRX lead to LCA and these mutations have been used in genetic complementation experiments with *Drosophila otd* to reveal differential effects of these mutations on rhodopsin gene expression and rhabdomeric structure (Terrell et al. 2012).

Concerning rhabdomeric structure, some *Drosophila* mutants have been particularly useful in elucidating how this impacts retinal degeneration. In particular, mutations affecting the Crumbs complex, formed by the proteins Stardust, Discs-lost/PATJ and Crumbs, were shown to disrupt the correct separation of the rhabdomere from the stalk membrane in photoreceptors (Fig. 3) (Berger et al. 2007; Hong et al. 2003; Pellikka et al. 2002; Richard et al. 2006). Furthermore, mutations affecting the GPI-anchored protein Chaoptin and the transmembrane protein Prominin along with its associated extracellular glycoprotein Eyes Shut prevent the separation of adjacent rhabdomeric membranes and disrupt the inter-rhabdomeral space (Fig. 3) (Cook and Zelhof 2008; Gurudev et al. 2014; Husain et al. 2006; Nie et al. 2012; Zelhof et al. 2006). These mutations result in light-dependent photoreceptor degeneration possibly as a direct consequent of loss of localisation of rhodopsin and other proteins to the rhabdomeric membrane. Indeed, these effects are similar to architectural defects seen in the rhabdomeres of null or strong mutants of *Drosophila* Rh1 (Kurada and O'Tousa 1995; Leonard et al. 1992). Importantly, Crumbs has been shown to interact and stabilize Myosin V and thereby promote trafficking of Rh1 to the rhabdomeres (Pocha et al. 2011). This mechanism may bear relevance to cases of autosomal recessive retinitis pigmentosa and LCA and autosomal dominant pigmented paravenous chorioretinal atrophy associated with mutations in the human *CRB1* gene (Cremers et al. 2002; den Hollander et al. 1999, 2001, 2010; Jacobson et al. 2003; Lotery et al. 2001; McKay et al. 2005), or in autosomal recessive retinal degeneration caused by mutation in human *PROMINI-1* (Maw et al. 2000), or *RP25*, the orthologue of *Drosophila Eyes Shut* (Abd El-Aziz et al. 2008; Alfano et al. 2016; Yu et al. 2016).

Critically, *Drosophila* research has contributed to highlight targets for therapeutical approaches to many of the degenerations reported above. The chemical transformations of dietary carotenoids into 3-hydroxyl, 11-*cis* retinal, were shown to be important modulators of light-induced retinal degeneration (Voolstra et al. 2010; Wang et al. 2010, 2012). Limiting de novo chromophore synthesis, via B-carotene/vitamin-A dietary depletion, can greatly reduce rhodopsin levels, thus significantly rescuing light-induced retinal degeneration in mutants affecting the stability of the metarhodopsin–Arrestin2 complex (Alloway et al. 2000; Berger et al. 2007; Kiselev et al. 2000; Richard et al. 2006), and similarly in *crumbs, stardust* and *PATJ* mutant eyes (Johnson et al. 2002).

On the other hand, in cases of accumulation of immature rhodopsin, a *Drosophila* study has shown that boosting ER-associated degradation (ERAD), by overexpression of the ERAD factors Hrd1 and EDEM2, reduces mutant Rh1 levels in dominant RhG69D mutants, thereby delaying retinal degeneration (Kang and Ryoo 2009). Intriguingly, genetic inactivation of the ERAD effector chaperone VCP/ter94 in *Drosophila* or its chemical inhibition with Eeyarestatin I led to strong suppression of retinal degeneration caused by accumulation of the immature RhP23H mutant (Griciuc et al. 2010). These apparently conflicting observations hint at different mechanisms of dominance of Rh1 mutations and argue that manipulation of ERAD for therapeutic purposes should consider these differences carefully. Similar to the effects observed for the manipulation of ERAD, potentiating autophagy or lysosomal degradation pathways can effectively reduce rhodopsin accumulation and ameliorate retinal degeneration (Lee et al. 2013; Wang et al. 2009).

A possible mechanism underlying the degeneration upon subcellular rhodopsin accumulation is an overload of cytoplasmic Ca^{2+} influx (Orrenius et al. 2003). Cytoplasmic Ca^{2+} influx induces the dephosphorylation of metarhodopsin by CAMKII and, therefore, low levels of Ca^{2+} can lead to accumulation of internalized metarhodopsin–arrestin complexes and cause photoreceptor degeneration (Chinchore et al. 2009; Kiselev et al. 2000; Orem and Dolph 2002). This is also seen in loss of function mutations in TRP calcium channels, but simultaneous counterbalancing mutations in the Ca^{2+}/Na^{2+} exchanger CalX or the diacylglycerol Kinase, RDGA, can greatly suppress light-induced retinal degeneration, indicating that balanced Ca^{2+} levels are critical for photoreceptor survival (Fig. 3) (Raghu et al. 2000; Wang et al. 2005). Cytoplasmic Ca^{2+} influx during the photo-response is modulated by the levels of PIP2 and their effect on calcium channels. Interestingly, an altered PIP2 regeneration cycle in *Drosophila* photoreceptors, such as through mutations affecting the Diacylglycerol Kinase, RDGA, or the phosphatidate phosphatase, Lazaro, or overexpression of phospholipase D, can all modify light-induced neurodegeneration phenotypes (Garcia-Murillas et al. 2006; Inoue et al. 1989; Kwon and Montell 2006; LaLonde et al. 2006; Masai et al. 1993).

It has been suggested that dominant negative mutations in rhodopsin associated with retinitis pigmentosa could be especially amenable to gene therapy, as providing extra dosage of rhodopsin was shown to significantly ameliorate the

cell death observed in the Rh P23H mouse model (Lewin et al. 2014; Mao et al. 2011). However, too much rhodopsin overexpression was also shown to cause retinal degeneration in this case, indicating that rhodopsin augmentation needs to be tightly controlled for therapeutic purposes. In *Drosophila*, it was also noticed that expression of phosphorylation-deficient rhodopsin could offer protective effects in *norpA* mutant photoreceptors, indicating that modulation of rhodopsin phosphorylation is critical to prevent its high levels of toxic internalization in light-dependent retinal degeneration (Kristaponyte et al. 2012).

With the advent of CRISPR/Cas9 technology, it is now possible to realize many of these gene therapy changes, albeit cautiously considering possible off-target effects. Recently, AAV-mediated CRISPR/Cas9 targeting of Nrl, a rod-specific transcription factor, was shown to improve rod survival in a mouse Rh P374S mutant (Yu et al. 2017). Furthermore, CRISPR/Cas9 targeting of the Rh P23H allele has been achieved efficiently in a null background both in the mouse and pig retina, offering a great promise for gene therapy (Burnight et al. 2017; Latella et al. 2016). Alternatively, using an artificial transcription factor, it was recently possible to repress a mutant rhodopsin gene in pigs, while maintaining normal expression of the wild-type rhodopsin (Botta et al. 2016).

Future perspectives

The genetic basis of most eye conditions, for example, anophthalmia and microphthalmia, has only been characterized in less than 30% of cases (Chassaing et al. 2014; Williamson and FitzPatrick 2014). This low rate of diagnosis is caused in part by the polygenic nature of eye development and by the fact that many cases are caused by rare variants. This is exacerbated by a poor understanding of the function of most human genes. Further functional analysis of known disease-causing genes and screens for new candidates in *Drosophila* has great potential to improve diagnosis and better understand the underlying mechanisms (Wangler et al. 2017). This was exemplified recently by an elegant screen in *Drosophila* for lethal mutations in genes involved in sensory functions and cross-referencing with human exome data (Yamamoto et al. 2014). This study allowed the diagnosis of conditions in several individuals including a new role for *Crx* in bull's eye maculopathy where the phenotypic effect on photoreceptors was similar in flies and humans (Yamamoto et al. 2014). This was facilitated by the availability of sophisticated approaches for screening and powerful tools for genetic and phenotypic analysis in this model. Therefore, it is clear that the *Drosophila* eye will continue to be an excellent and economic model to study eye conditions as well as other diseases (Chow and Reiter 2017; Kumar 2018; Senturk and Bellen 2017; Yamamoto et al. 2014). This can be enhanced by further collaborations between clinicians and researchers working on *Drosophila* (Wangler et al. 2015) as part of national and international initiatives such as the Undiagnosed Diseases Network (Gahl et al. 2016) and tools such as GeneMatcher (Sobreira et al. 2015a, b).

Acknowledgements PG and APM were funded by BBSRC Grant BB/M020967/1. IA has received funding from *Apoyo a Unidades de Excelencia María de Maeztu* from the Ministry of Economy, Industry and Competitiveness of Spain.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Abd El-Aziz MM, Barragan I, O'Driscoll CA, Goodstadt L, Prigmore E, Borrego S, Mena M, Pieras JI, El-Ashry MF, Safieh LA, Shah A, Cheetham ME, Carter NP, Chakarova C, Ponting CP, Bhattacharya SS, Antinolo G (2008) EYS, encoding an ortholog of Drosophila spacemaker, is mutated in autosomal recessive retinitis pigmentosa. Nat Genet 40:1285–1287. https://doi.org/10.1038/ng.241

Adams MD, Celniker SE, Holt RA, Evans CA, Gocayne JD, Amanatides PG, Scherer SE, Li PW, Hoskins RA, Galle RF, George RA, Lewis SE, Richards S, Ashburner M, Henderson SN, Sutton GG, Wortman JR, Yandell MD, Zhang Q, Chen LX, Brandon RC, Rogers YH, Blazej RG, Champe M, Pfeiffer BD, Wan KH, Doyle C, Baxter EG, Helt G, Nelson CR, Gabor GL, Abril JF, Agbayani A, An HJ, Andrews-Pfannkoch C, Baldwin D, Ballew RM, Basu A, Baxendale J, Bayraktaroglu L, Beasley EM, Beeson KY, Benos PV, Berman BP, Bhandari D, Bolshakov S, Borkova D, Botchan MR, Bouck J, Brokstein P, Brottier P, Burtis KC, Busam DA, Butler H, Cadieu E, Center A, Chandra I, Cherry JM, Cawley S, Dahlke C, Davenport LB, Davies P, de Pablos B, Delcher A, Deng Z, Mays AD, Dew I, Dietz SM, Dodson K, Doup LE, Downes M, Dugan-Rocha S, Dunkov BC, Dunn P, Durbin KJ, Evangelista CC, Ferraz C, Ferriera S, Fleischmann W, Fosler C, Gabrielian AE, Garg NS, Gelbart WM, Glasser K, Glodek A, Gong F, Gorrell JH, Gu Z, Guan P, Harris M, Harris NL, Harvey D, Heiman TJ, Hernandez JR, Houck J, Hostin D, Houston KA, Howland TJ, Wei MH, Ibegwam C et al (2000) The genome sequence of Drosophila melanogaster. Science 287:2185–2195

Ahmed M, Wong EYM, Sun J, Xu J, Wang F, Xu PX (2012) Eya1-Six1 interaction is sufficient to induce hair cell fate in the cochlea by activating atoh1 expression in cooperation with Sox2. Dev Cell 22:377–390. https://doi.org/10.1016/j.devcel.2011.12.006

Aldahmesh MA, Khan AO, Hijazi H, Alkuraya FS (2013) Homozygous truncation of SIX6 causes complex microphthalmia in humans. Clin Genet 84:198–199. https://doi.org/10.1111/cge.12046

Aldaz S, Morata G, Azpiazu N (2003) The Pax-homeobox gene eyegone is involved in the subdivision of the thorax of Drosophila. Dev (Camb Engl) 130:4473–4482. https://doi.org/10.1242/dev.00643

Alemaghtheh M, Gregory C, Inglehearn C, Hardcastle A, Bhattacharya S (1993) Rhodopsin mutations in autosomal dominant retinitis pigmentma. Hum Mutat 255:249–255

Alfano G, Kruczek PM, Shah AZ, Kramarz B, Jeffery G, Zelhof AC, Bhattacharya SS (2016) EYS is a protein associated with the

ciliary axoneme in rods and cones. PLoS One 11:1–20. https://doi.org/10.1371/journal.pone.0166397

Ali MU, Rahman MSU, Cao J, Yuan PX (2017) Genetic characterization and disease mechanism of retinitis pigmentosa; current scenario. 3 Biotech 7:251. https://doi.org/10.1007/s13205-017-0878-3

Alloway PG, Howard L, Dolph PJ (2000) The formation of stable rhodopsin-arrestin complexes induces apoptosis and photoreceptor cell degeneration. Neuron 28:129–138. https://doi.org/10.1016/S0896-6273(00)00091-X

Anderson J, Salzer CL, Kumar JP (2006) Regulation of the retinal determination gene dachshund in the embryonic head and developing eye of Drosophila. Dev Biol 297:536–549. https://doi.org/10.1016/j.ydbio.2006.05.004

Atkins M, Jiang Y, Sansores-Garcia L, Jusiak B, Halder G, Mardon G (2013) Dynamic rewiring of the Drosophila retinal determination network switches its function from selector to differentiation. PLoS Genet 9. https://doi.org/10.1371/journal.pgen.1003731

Azuma N, Hirakiyama A, Inoue T, Asaka A, Yamada M (2000) Mutations of a human homologue of the Drosophila eyes absent gene (EYA1) detected in patients with congenital cataracts and ocular anterior segment anomalies. Hum Mol Genet 9:363–366

Belecky-Adams T, Tomarev S, Li HS, Ploder L, McInnes RR, Sundin O, Adler R (1997) Pax-6, Prox 1, and Chx10 homeobox gene expression correlates with phenotypic fate of retinal precursor cells. Invest Ophthalmol Vis Sci 38:1293–1303

Bentrop J (1998) Rhodopsin mutations as the cause of retinal degeneration - Classification of degeneration phenotypes in the model system Drosophila melanogaster. Acta Anat 162:85–94. https://doi.org/10.1159/000046472

Benzer S (1967) Behavioral mutants of Drosophila isolated by countercurrent distribution. Proc Natl Acad Sci USA 58:1112–1119

Berger S, Bulgakova NA, Grawe F, Johnson K, Knust E (2007) Unraveling the genetic complexity of Drosophila stardust during photoreceptor morphogenesis and prevention of light-induced degeneration. Genetics 176:2189–2200. https://doi.org/10.1534/genetics.107.071449

Bessa J, Casares F (2005) Restricted teashirt expression confers eye-specific responsiveness to Dpp and Wg signals during eye specification in Drosophila. Development 132:5011–5020. https://doi.org/10.1242/dev.02082

Bessa J, Carmona L, Casares F (2009) Zinc-finger paralogues tsh and tio are functionally equivalent during imaginal development in Drosophila and maintain their expression levels through auto- and cross-negative feedback loops. Dev Dyn 238:19–28. https://doi.org/10.1002/dvdy.21808

Bhattacharya S, Lester D, Keen J, Bashir R, Lauffart B, Inglehearn C, Jay M, Bird A (1991) Retinitis pigmentosa and mutations in rhodopsin. The Lancet 337:185. https://doi.org/10.1016/0140-6736(91)90858-M

Blanco J, Girard F, Kamachi Y, Kondoh H, Gehring WJ (2005) Functional analysis of the chicken delta1-crystallin enhancer activity in Drosophila reveals remarkable evolutionary conservation between chicken and fly. Development 132:1895–1905. https://doi.org/10.1242/dev.01738

Bonini NM, Leiserson WM, Benzer S (1993) The eyes absent gene: genetic control of cell survival and differentiation in the developing Drosophila eye. Cell 72:379–395. https://doi.org/10.1016/0092-8674(93)90115-7

Bonini NM, Bui QT, Gray-Board GL, Warrick JM (1997) The Drosophila eyes absent gene directs ectopic eye formation in a pathway conserved between flies and vertebrates. Development 124:4819–4826

Borst A (2009) Drosophila's view on insect vision. Curr Biol 19:R36–R47. https://doi.org/10.1016/j.cub.2008.11.001

Botta S, Marrocco E, de Prisco N, Curion F, Renda M, Sofia M, Lupo M, Carissimo A, Bacci ML, Gesualdo C, Rossi S, Simonelli F, Surace EM (2016) Rhodopsin targeted transcriptional silencing by DNA-binding. eLife 5:1–14. https://doi.org/10.7554/eLife.12242

Bras-Pereira C, Casares F, Janody F (2015) The retinal determination gene dachshund restricts cell proliferation by limiting the activity of the Homothorax-Yorkie complex. Development 142:1470–1479. https://doi.org/10.1242/dev.113340

Brzezinski JAT, Prasov L, Glaser T (2012) Math5 defines the ganglion cell competence state in a subpopulation of retinal progenitor cells exiting the cell cycle. Dev Biol 365:395–413. https://doi.org/10.1016/j.ydbio.2012.03.006

Burke C, Trinh K, Nadar V, Sanyal S (2017) AxGxE: using flies to interrogate the complex etiology of neurodegenerative disease. Curr Top Dev Biol 121:225–251. https://doi.org/10.1016/bs.ctdb.2016.07.007

Burnight ER, Gupta M, Wiley LA, Anfinson KR, Tran A, Triboulet R, Hoffmann JM, Klaahsen DL, Andorf JL, Jiao C, Sohn EH, Adur MK, Ross JW, Mullins RF, Daley GQ, Schlaeger TM, Stone EM, Tucker BA (2017) Using CRISPR-Cas9 to generate gene-corrected autologous iPSCs for the treatment of inherited retinal degeneration. Mol Ther 25:1999–2013. https://doi.org/10.1016/j.ymthe.2017.05.015

Cagan R (2009) Principles of Drosophila eye differentiation. Curr Top Dev Biol 89: 115 – 35. https://doi.org/10.1016/s0070-2153(09)89005-4

Canto-Soler MV, Huang H, Romero MS, Adler R (2008) Transcription factors CTCF and Pax6 are segregated to different cell types during retinal cell differentiation. Dev Dyn 237:758–767. https://doi.org/10.1002/dvdy.21420

Casares F, Almudi I (2016) Fast and Furious 800. the retinal determination gene network in drosophila. In: Castelli-Gair Hombría J, Bovolenta P (eds) Organogenetic gene networks: genetic control of organ formation. Springer International Publishing, Cham, pp 95–124

Chang GQ, Hao Y, Wong F (1993) Apoptosis: final common pathway of photoreceptor death in rd, rds, and rhodopsin mutant mice. Neuron 11:595–605

Chao J-L (2004) Localized Notch signal acts through eyg and upd to promote global growth in Drosophila eye. Development 131:3839–3847. https://doi.org/10.1242/dev.01258

Charlton-Perkins M, Brown NL, Cook TA (2011) The lens in focus: a comparison of lens development in Drosophila and vertebrates. Mol Genet Genomics 286:189–213. https://doi.org/10.1007/s00438-011-0643-y

Chassaing N, Causse A, Vigouroux A, Delahaye A, Alessandri JL, Boespflug-Tanguy O, Boute-Benejean O, Dollfus H, Duban-Bedu B, Gilbert-Dussardier B, Giuliano F, Gonzales M, Holder-Espinasse M, Isidor B, Jacquemont ML, Lacombe D, Martin-Coignard D, Mathieu-Dramard M, Odent S, Picone O, Pinson L, Quelin C, Sigaudy S, Toutain A, Thauvin-Robinet C, Kaplan J, Calvas P (2014) Molecular findings and clinical data in a cohort of 150 patients with anophthalmia/microphthalmia. Clin Genet 86:326–334. https://doi.org/10.1111/cge.12275

Chen R, Amoui M, Zhang Z, Mardon G (1997) Dachshund and eyes absent proteins form a complex and function synergistically to induce ectopic eye development in Drosophila. Cell 91:893–903. https://doi.org/10.1016/S0092-8674(00)80481-X

Chen CK, Burns ME, Spencer M, Niemi GA, Chen J, Hurley JB, Baylor DA, Simon MI (1999) Abnormal photoresponses and light-induced apoptosis in rods lacking rhodopsin kinase. Proc Natl Acad Sci USA 96:3718–3722

Chen J, Shi G, Concepcion FA, Xie G, Oprian D, Chen J (2006) Stable rhodopsin/arrestin complex leads to retinal degeneration in a transgenic mouse model of autosomal dominant

retinitis pigmentosa. J Neurosci 26:11929–11937. https://doi.org/10.1523/jneurosci.3212-06.2006
Chen K, Wu K, Cai S, Zhang W, Zhou J, Wang J, Ertel A, Li Z, Rui H, Quong A, Lisanti MP, Tozeren A, Tanes C, Addya S, Gormley M, Wang C, McMahon SB, Pestell RG (2013) Dachshund binds p53 to block the growth of lung adenocarcinoma cells. Can Res 73:3262–3274. https://doi.org/10.1158/0008-5472.CAN-12-3191
Cheng H, Khanna H, Oh EC, Hicks D, Mitton KP, Swaroop A (2004) Photoreceptor-specific nuclear receptor NR2E3 functions as a transcriptional activator in rod photoreceptors. Hum Mol Genet 13:1563–1575. https://doi.org/10.1093/hmg/ddh173
Cheyette BNR, Green PJ, Martin K, Garren H, Hartenstein V, Zipursky SL (1994) The drosophila sine oculis locus encodes a homeodomain-containing protein required for the development of the entire visual system. Neuron 12:977–996. https://doi.org/10.1016/0896-6273(94)90308-5
Chinchore Y, Mitra A, Dolph PJ (2009) Accumulation of rhodopsin in late endosomes triggers photoreceptor cell degeneration. PLoS Genet 5. https://doi.org/10.1371/journal.pgen.1000377
Chow CY, Reiter LT (2017) Etiology of Human Genetic Disease on the Fly. Trends Genet 33:391–398. https://doi.org/10.1016/j.tig.2017.03.007
Chu Q, Han N, Yuan X, Nie X, Wu H, Chen Y, Guo M, Yu S, Wu K (2014) DACH1 inhibits cyclin D1 expression, cellular proliferation and tumor growth of renal cancer cells. J Hematol Oncol 7:73. https://doi.org/10.1186/s13045-014-0073-5
Colley NJ, Cassill JA, Baker EK, Zuker CS (1995) Defective Intracellular Transport is the Molecular Basis of Rhodopsin- Dependent Dominant Retinal Degeneration. Proc Natl Acad Sci USA 92:3070–3074
Cook B, Zelhof AC (2008) Photoreceptors in evolution and disease. Nat Genet 40:1275–1276. https://doi.org/10.1038/ng1108-1275
Cornish EE, Madigan MC, Natoli R, Hales A, Hendrickson AE, Provis JM (2005) Gradients of cone differentiation and FGF expression during development of the foveal depression in macaque retina. Vis Neurosci 22:447–459. https://doi.org/10.1017/s0952523805224069
Cremers FPM, van den Hurk JAJM, den Hollander AI (2002) Molecular genetics of Leber congenital amaurosis. Human Mol genet 11:1169–1176. https://doi.org/10.1093/hmg/11.10.1169
Crowley MA, Conlin LK, Zackai EH, Deardorff MA, Thiel BD, Spinner NB (2010) Further evidence for the possible role of MEIS2 in the development of cleft palate and cardiac septum. Am J Med Genet A 152A:1326–1327. https://doi.org/10.1002/ajmg.a.33375
Czerny T, Halder G, Kloter U, Souabni A, Gehring WJ, Busslinger M (1999) Twin of eyeless, a second Pax-6 gene of Drosophila, acts upstream of eyeless in the control of eye development. Mol Cell 3:297–307. https://doi.org/10.1016/S1097-2765(00)80457-8
Daiger SP, Bowne SJ, Sullivan LS (2007) Perspective on genes and mutations causing retinitis pigmentosa. Arch Ophthalmol 125:151–158. https://doi.org/10.1001/archopht.125.2.151
Datta RR, Lurye JM, Kumar JP (2009) Restriction of ectopic eye formation by Drosophila teashirt and tiptop to the developing antenna. Dev Dyn 238:2202–2210. https://doi.org/10.1002/dvdy.21927
Davis TL, Rebay I (2017) Master regulators in development: Views from the Drosophila retinal determination and mammalian pluripotency gene networks. Dev Biol 421:93–107. https://doi.org/10.1016/j.ydbio.2016.12.005
de Melo J, Peng GH, Chen S, Blackshaw S (2011) The Spalt family transcription factor Sall3 regulates the development of cone photoreceptors and retinal horizontal interneurons. Development 138:2325–2336. https://doi.org/10.1242/dev.061846
den Hollander AI, Ten Brink JB, De Kok YJM, Van Soest S, Van Den Born LI, Van Driel MA, Van De Pol DJR, Payne AM, Bhattacharya SS, Kellner U, Hoyng CB, Westerveld A, Brunner HG, Bleeker-Wagemakers EM, Deutman AF, Heckenlively JR, Cremers FPM, Bergen AAB (1999) Mutations in a human homologue of Drosophila crumbs cause retinitis pigmentosa (RP12). Nat Genet 23:217–221. https://doi.org/10.1038/13848
den Hollander AI, Heckenlively JR, van den Born LI, de Kok YJ, van der Velde-Visser SD, Kellner U, Jurklies B, van Schooneveld MJ, Blankenagel A, Rohrschneider K, Wissinger B, Cruysberg JR, Deutman AF, Brunner HG, Apfelstedt-Sylla E, Hoyng CB, Cremers FP (2001) Leber congenital amaurosis and retinitis pigmentosa with coats-like exudative vasculopathy are associated with mutations in the crumbs homologue 1 (CRB1) gene. Am J Human Genet 69:198–203. https://doi.org/10.1086/321263
den Hollander AI, Biyanwila J, Kovach P, Bardakjian T, Traboulsi EI, Ragge NK, Schneider A, Malicki J (2010) Genetic defects of GDF6 in the zebrafish out of sight mutant and in human eye developmental anomalies. BMC Genet 11:102. https://doi.org/10.1186/1471-2156-11-102
Desplan C (1997) Eye development: Governed by a dictator or a junta? Cell 91:861–864. https://doi.org/10.1016/S0092-8674(00)80475-4
Dolph PJ, Ranganathan R, Colley NJ, Hardy RW, Socolich M, Zuker CS (1993) Arrestin function in inactivation of G protein-coupled receptor rhodopsin in vivo. Science 260:1910–1916
Dominguez M, de Celis JF (1998) A dorsal/ventral boundary established by Notch controls growth and polarity in the Drosophila eye. Nature 396:276–278
Dominguez M, Ferres-Marco D, Gutierrez-Aviño FJ, Speicher SA, Beneyto M (2004) Growth and specification of the eye are controlled independently by eyegone and eyeless in Drosophila melanogaster. Nat Genet 36:31–39. https://doi.org/10.1038/ng1281
Dryja TP (2000) Molecular genetics of oguchi disease, fundus albipunctatus, and other forms of stationary night blindness: LVII Edward Jackson Memorial Lecture. Am J Ophthalmol 130:547–563. https://doi.org/10.1016/S0002-9394(00)00737-6
Dryja TP, McGee TL, Reichel E, Hahn LB, Cowley GS, Yandell DW, Sandberg MA, Berson EL (1990) A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature 343:364–366. https://doi.org/10.1038/343364a0
Dryja TP, Hahn LB, Cowley GS, McGee TL, Berson EL (1991) Mutation spectrum of the rhodopsin gene among patients with autosomal dominant retinitis pigmentosa. Proc Natl Acad Sci USA 88:9370–9374
Favor J, Sandulache R, Neuhäuser-Klaus A, Pretsch W, Chatterjee B, Senft E, Wurst W, Blanquet V, Grimes P, Spörle R, Schughart K (1996) The mouse Pax2(1Neu) mutation is identical to a human PAX2 mutation in a family with renal-coloboma syndrome and results in developmental defects of the brain, ear, eye, and kidney. Proc Natl Acad Sci USA 93:13870–13875. https://doi.org/10.1073/pnas.93.24.13870
Frankfort BJ, Mardon G (2002) R8 development in the Drosophila eye: a paradigm for neural selection and differentiation. Development 129:1295–1306
Freeman M (1996) Reiterative use of the EGF receptor triggers differentiation of all cell types in the Drosophila eye. Cell 87:651–660. https://doi.org/10.1016/S0092-8674(00)81385-9
Freeman M (1997) Cell determination strategies in the Drosophila eye. Development 124:261–270
Freund CL, Gregory-Evans CY, Furukawa T, Papaioannou M, Looser J, Ploder L, Bellingham J, Ng D, Herbrick JA, Duncan A, Scherer SW, Tsui LC, Loutradis-Anagnostou A, Jacobson SG, Cepko CL, Bhattacharya SS, McInnes RR (1997) Cone-rod dystrophy due to mutations in a novel photoreceptor-specific homeobox gene (CRX) essential for maintenance of the photoreceptor. Cell 91:543–553
Freund CL, Wang QL, Chen S, Muskat BL, Wiles CD, Sheffield VC, Jacobson SG, McInnes RR, Zack DJ, Stone EM (1998) De

novo mutations in the CRX homeobox gene associated with Leber congenital amaurosis. Nat Genet 18:311–312. https://doi.org/10.1038/ng0498-311

Fried P, Sanchez-Aragon M, Aguilar-Hidalgo D, Lehtinen B, Casares F, Iber D (2016) A Model of the spatio-temporal dynamics of Drosophila eye disc development. PLoS Comput Biol 12:e1005052. https://doi.org/10.1371/journal.pcbi.1005052

Fu W, Duan H, Frei E, Noll M (1998) Shaven and sparkling are mutations in separate enhancers of the Drosophila Pax2 homolog. Development 125:2943–2950

Gahl WA, Mulvihill JJ, Toro C, Markello TC, Wise AL, Ramoni RB, Adams DR, Tifft CJ (2016) The NIH undiagnosed diseases program and network: applications to modern medicine. Mol Genet Metab 117:393–400. https://doi.org/10.1016/j.ymgme.2016.01.007

Garcia-Murillas I, Pettitt T, Macdonald E, Okkenhaug H, Georgiev P, Trivedi D, Hassan B, Wakelam M, Raghu P (2006) Lazaro encodes a lipid phosphate phosphohydrolase that regulates phosphatidylinositol turnover during Drosophila phototransduction. Neuron 49:533–546. https://doi.org/10.1016/j.neuron.2006.02.001

Gehring WJ (1996) The master control gene for morphogenesis and evolution of the eye. Genes Cells. 1: 11–5. https://doi.org/10.1046/j.1365-2443.1996.11011.x

Gehring WJ (2005) New perspectives on eye development and the evolution of eyes and photoreceptors. J Hered 96:171–184. https://doi.org/10.1093/jhered/esi027

Gehring WJ (2014) The evolution of vision. Wiley Interdiscip Rev. 3:1–40. https://doi.org/10.1002/wdev.96

Ghiasvand NM, Rudolph DD, Mashayekhi M, Brzezinski JAT, Goldman D, Glaser T (2011) Deletion of a remote enhancer near ATOH7 disrupts retinal neurogenesis, causing NCRNA disease. Nat Neurosci 14:578–586. https://doi.org/10.1038/nn.2798

Glaser T, Walton DS, Maas RL (1992) Genomic structure, evolutionary conservation and aniridia mutations in the human PAX6 gene. Nat Genet 2:232–239. https://doi.org/10.1038/ng1192-232

Glaser T, Jepeal L, Edwards JG, Young SR, Favor J, Maas RL (1994) PAX6 gene dosage effect in a family with congenital cataracts, aniridia, anophthalmia and central nervous system defects. Nat Genet 7:463–471. https://doi.org/10.1038/ng0894-463

Green P, Hartenstein AY, Hartenstein V (1993) The embryonic development of the Drosophila visual system. Cell Tissue Res 273:583–598

Griciuc A, Aron L, Roux MJ, Klein R, Giangrande A, Ueffing M (2010) Inactivation of VCP/ter94 suppresses retinal pathology caused by misfolded Rhodopsin in Drosophila. PLoS Genet 6. https://doi.org/10.1371/journal.pgen.1001075

Gurudev N, Yuan M, Knust E (2014) Chaoptin, prominin, eyes shut and crumbs form a genetic network controlling the apical compartment of Drosophila photoreceptor cells. Biology Open 3:332–341. https://doi.org/10.1242/bio.20147310

Halder G, Callaerts P, Gehring W (1995) Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila. Science 267:1788–1792. https://doi.org/10.1126/science.7892602

Halder G, Callaerts P, Flister S, Walldorf U, Kloter U, Gehring WJ (1998) Eyeless initiates the expression of both sine oculis and eyes absent during Drosophila compound eye development. Dev (Camb Engl) 125:2181–2191

Hanson IM, Fletcher JM, Jordan T, Brown A, Taylor D, Adams RJ, Punnett HH, van Heyningen V (1994) Mutations at the PAX6 locus are found in heterogeneous anterior segment malformations including Peters' anomaly. Nat Genet 6:168–173. https://doi.org/10.1038/ng0294-168

Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, Mizushima N (2006) Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 441:885–889. https://doi.org/10.1038/nature04724

Harris WA, Stark WS (1977) Hereditary retinal degeneration in Drosophila melanogaster. A mutant defect associated with the phototransduction process. J Gen Physiol 69: 261–291. https://doi.org/10.1085/jgp.69.3.261

Harris WA, Stark WS, Walker JA (1976) genetic dissection of photoreceptor system in compound eye of *Drosophila melanogaster*. J Physiol-Lond 256:415–415&

Heberlein U, Singh CM, Luk AY, Donohoe TJ (1995) Growth and differentiation in the Drosophila eye coordinated by hedgehog. Nature 373:709–711. https://doi.org/10.1038/373709a0

Heberlein U, Borod ER, Chanut FA (1998) Dorsoventral patterning in the Drosophila retina by wingless. Development 125:567–577

Hendrickson A, Bumsted-O'Brien K, Natoli R, Ramamurthy V, Possin D, Provis J (2008) Rod photoreceptor differentiation in fetal and infant human retina. Exp Eye Res 87:415–426. https://doi.org/10.1016/j.exer.2008.07.016

Hennig AK, Peng GH, Chen S (2008) Regulation of photoreceptor gene expression by Crx-associated transcription factor network. Brain Res 1192:114–133. https://doi.org/10.1016/j.brainres.2007.06.036

Hilbrant M, Almudi I, Leite DJ, Kuncheria L, Posnien N, Nunes MDS, McGregor AP (2014) Sexual dimorphism and natural variation within and among species in the Drosophila retinal mosaic. BMC Evol Biol 14:240

Hong Y, Ackerman L, Jan LY, Jan Y-N (2003) Distinct roles of Bazooka and Stardust in the specification of Drosophila photoreceptor membrane architecture. Proc Natl Acad Sci USA 100:12712–12717. https://doi.org/10.1073/pnas.2135347100

Hoskins BE, Cramer CH, Silvius D, Zou D, Raymond RM, Orten DJ, Kimberling WJ, Smith RJ, Weil D, Petit C, Otto EA, Xu PX, Hildebrandt F (2007) Transcription factor SIX5 is mutated in patients with branchio-oto-renal syndrome. Am J Hum Genet 80:800–804. https://doi.org/10.1086/513322

Hotta Y, Benzer S (1970) Genetic dissection of the Drosophila nervous system by means of mosaics. Proc Natl Acad Sci USA 67:1156–1163

Husain N, Pellikka M, Hong H, Klimentova T, Choe KM, Clandinin TR, Tepass U (2006) The Agrin/Perlecan-related protein eyes shut is essential for epithelial lumen formation in the Drosophila retina. Dev Cell 11:483–493. https://doi.org/10.1016/j.devcel.2006.08.012

Iakhine R (2004) Novel dominant rhodopsin mutation triggers two mechanisms of retinal degeneration and photoreceptor desensitization. J Neurosci 24:2516–2526. https://doi.org/10.1523/JNEUROSCI.5426-03.2004

Inoue H, Yoshioka T, Hotta Y (1989) Diacylglycerol kinase defect in a Drosophila retinal degeneration mutant rdgA. J Biol Chem 264:5996–6000

Jacobson SG, Cideciyan AV, Aleman TS, Pianta MJ, Sumaroka A, Schwartz SB, Smilko EE, Milam AH, Sheffield VC, Stone EM (2003) Crumbs homolog 1 (CRB1) mutations result in a thick human retina with abnormal lamination. Hum Mol Genet 12:1073–1078. https://doi.org/10.1093/hmg/ddg117

Jang C-C, Chao J-L, Jones N, Yao L-C, Bessarab DA, Kuo YM, Jun S, Desplan C, Beckendorf SK, Sun YH (2003) Two Pax genes, eye gone and eyeless, act cooperatively in promoting Drosophila eye development. Dev (Camb Engl) 130:2939–2951. https://doi.org/10.1242/dev.00522

Janody F, Lee JD, Jahren N, Hazelett DJ, Benlali A, Miura GI, Draskovic I, Treisman JE (2004) A mosaic genetic screen reveals distinct roles for trithorax and polycomb group genes in Drosophila eye development. Genetics 166:187–200. https://doi.org/10.1534/genetics.166.1.187

Jarman AP, Grell EH, Ackerman L, Jan LY, Jan YN (1994) Atonal is the proneural gene for Drosophila photoreceptors. Nature 369:398–400

Jarman AP, Sun Y, Jan LY, Jan YN (1995) Role of the proneural gene, atonal, in formation of Drosophila chordotonal organs and photoreceptors. Development 121:2019–2030

Jemc J, Rebay I (2007) Identification of transcriptional targets of the dual-function transcription factor/phosphatase eyes absent. Dev Biol 310:416–429. https://doi.org/10.1016/j.ydbio.2007.07.024

Johnson K, Grawe F, Grzeschik N, Knust E (2002) Drosophila crumbs is required to inhibit light-induced photoreceptor degeneration. Curr Biol 12:1675–1680. https://doi.org/10.1016/S0960-9822(02)01180-6

Johnston RJ Jr, Otake Y, Sood P, Vogt N, Behnia R, Vasiliauskas D, McDonald E, Xie B, Koenig S, Wolf R, Cook T, Gebelein B, Kussell E, Nakagoshi H, Desplan C (2011) Interlocked feedforward loops control cell-type-specific rhodopsin expression in the Drosophila eye. Cell 145:956–968. https://doi.org/10.1016/j.cell.2011.05.003

Jonas JB, Schneider U, Naumann GO (1992) Count and density of human retinal photoreceptors. Graefes Arch Clin Exp Ophthalmol 230:505–510

Jordan T, Hanson I, Zaletayev D, Hodgson S, Prosser J, Seawright A, Hastie N, van Heyningen V (1992) The human PAX6 gene is mutated in two patients with aniridia. Nat Genet 1:328–332. https://doi.org/10.1038/ng0892-328

Jun S, Wallen RV, Goriely A, Kalionis B, Desplan C (1998) Lune/eye gone, a Pax-like protein, uses a partial paired domain and a homeodomain for DNA recognition. Proc Natl Acad Sci USA 95:13720–13725. https://doi.org/10.1073/pnas.95.23.13720

Kaplan J, Rozet JM (2008) Eye disorders: hereditary. In: eLS. Wiley, Chichester. https://doi.org/10.1002/9780470015902.a0005510.pub2

Kaewkhaw R, Kaya KD, Brooks M, Homma K, Zou J, Chaitankar V, Rao M, Swaroop A (2015) Transcriptome dynamics of developing photoreceptors in three-dimensional retina cultures recapitulates temporal sequence of human cone and rod differentiation revealing cell surface markers and gene networks. Stem Cells 33:3504–3518. https://doi.org/10.1002/stem.2122

Kang M-J, Ryoo HD (2009) Suppression of retinal degeneration in Drosophila by stimulation of ER-associated degradation. Proc Natl Acad Sci USA 106:17043–17048. https://doi.org/10.1073/pnas.0905566106

Kenyon KL, Ranade SS, Curtiss J, Mlodzik M, Pignoni F (2003) Coordinating proliferation and tissue specification to promote regional identity in the Drosophila head. Dev Cell 5:403–414

Kiselev A, Socolich M, Vinós J, Hardy RW, Zuker CS, Ranganathan R (2000) A molecular pathway for light-dependent photoreceptor apoptosis in Drosophila. Neuron 28:139–152. https://doi.org/10.1016/S0896-6273(00)00092-1

Klesert TR, Cho DH, Clark JI, Maylie J, Adelman J, Snider L, Yuen EC, Soriano P, Tapscott SJ (2000) Mice deficient in Six5 develop cataracts: implications for myotonic dystrophy. Nat Genet 25:105–109. https://doi.org/10.1038/75490

Komatsu M, Waguri S, Chiba T, Murata S, Iwata JI, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, Tanaka K (2006) Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 441:880–884. https://doi.org/10.1038/nature04723

Kozmik Z, Daube M, Frei E, Norman B, Kos L, Dishaw LJ, Noll M, Piatigorsky J (2003) Role of Pax genes in eye evolution: a cnidarian PaxB gene uniting Pax2 and Pax6 functions. Dev Cell 5:773–785

Kreipke RE, Kwon YV, Shcherbata HR, Ruohola-Baker H (2017) Drosophila melanogaster as a model of muscle degeneration disorders. Curr Top Dev Biol 121:83–109. https://doi.org/10.1016/bs.ctdb.2016.07.003

Kristaponyte I, Hong Y, Lu H, Shieh B-H (2012) Role of rhodopsin and arrestin phosphorylation in retinal degeneration of Drosophila. J Neurosci 32:10758–10766. https://doi.org/10.1523/JNEUROSCI.0565-12.2012

Kumar JP (2011) My what big eyes you have: how the Drosophila retina grows. Dev Neurobiol 71:1133–1152. https://doi.org/10.1002/dneu.20921

Kumar JP (2012) Building an ommatidium one cell at a time. Dev Dyn 241:136–149. https://doi.org/10.1002/dvdy.23707

Kumar JP (2018) The fly eye: through the looking glass. Dev Dyn 247:111–123. https://doi.org/10.1002/dvdy.24585

Kumar JP, Moses K (2001) Expression of evolutionarily conserved eye specification genes during Drosophila embryogenesis. Dev Genes Evol 211:406–414. https://doi.org/10.1007/s004270100177

Kumar JP, Tio M, Hsiung F, Akopyan S, Gabay L, Seger R, Shilo BZ, Moses K (1998) Dissecting the roles of the Drosophila EGF receptor in eye development and MAP kinase activation. Development 125:3875–3885

Kurada P, O'Tousa JE (1995) Retinal degeneration caused by dominant rhodopsin mutations in Drosophila. Neuron 14:571–579. https://doi.org/10.1016/0896-6273(95)90313-5

Kwon Y, Montell C (2006) Dependence on the Lazaro phosphatidic acid phosphatase for the maximum light response. Curr Biol 16:723–729. https://doi.org/10.1016/j.cub.2006.02.057

LaLonde M, Janssens H, Yun S, Crosby J, Redina O, Olive V, Altshuller YM, Choi SY, Du G, Gergen JP, Frohman MA (2006) A role for phospholipase D in Drosophila embryonic cellularization. BMC Dev Biol 6:1–13. https://doi.org/10.1186/1471-213X-6-60

Land MF (2005) The optical structures of animal eyes. Curr Biol 15:R319–R323. https://doi.org/10.1016/j.cub.2005.04.041

Latella MC, Di Salvo MT, Cocchiarella F, Benati D, Grisendi G, Comitato A, Marigo V, Recchia A (2016) In vivo editing of the human mutant rhodopsin gene by electroporation of plasmid-based CRISPR/Cas9 in the mouse retina. Mol Ther Nucleic Acids 5:e389. https://doi.org/10.1038/mtna.2016.92

Laugier E, Yang Z, Fasano L, Kerridge S, Vola C (2005) A critical role of teashirt for patterning the ventral epidermis is masked by ectopic expression of tiptop, a paralog of teashirt in Drosophila. Dev Biol 283:446–458. https://doi.org/10.1016/j.ydbio.2005.05.005

Lee JD, Treisman JE (2002) Regulators of the morphogenetic furrow. In: Moses K (ed) Drosophila eye development. Springer Berlin Heidelberg, Berlin, pp 21–33

Lee JJ, von Kessler DP, Parks S, Beachy PA (1992) Secretion and localized transcription suggest a role in positional signaling for products of the segmentation gene hedgehog. Cell 71:33–50

Lee RD, Thomas CF, Marietta RG, Stark WS (1996) Vitamin A, visual pigments, and visual receptors in Drosophila. Microsc Res Tech 35: 418–430. 10.1002/(SICI)1097-0029(19961215)35:6<418::AID-JEMT2>3.0.CO;2-E

Lee J, Song M, Hong S (2013) Negative regulation of the novel norpAP24 Suppressor, diehard4, in the endo-lysosomal trafficking underlies photoreceptor cell degeneration. PLoS Genet 9. https://doi.org/10.1371/journal.pgen.1003559

Leonard DS, Bowman VD, Ready DF, Pak WL (1992) Degeneration of photoreceptors in rhodopsin mutants of Drosophila. J Neurobiol 23:605–626. https://doi.org/10.1002/neu.480230602

Lewin AS, Rossmiller B, Mao H (2014) Gene augmentation for adRP mutations in RHO. Cold Spring Harbor Perspect Med 4:1–13. https://doi.org/10.1101/cshperspect.a017400

Li X, Perissi V, Liu F, Rose DW, Rosenfeld MG (2002) Tissue-specific regulation of retinal and pituitary precursor cell

proliferation. Science 297:1180–1183. https://doi.org/10.1126/science.1073263

Li X, Oghi KA, Zhang J, Krones A, Bush KT, Glass CK, Nigam SK, Aggarwal AK, Maas R, Rose DW, Rosenfeld MG (2003) Eya protein phosphatase activity regulates Six1-Dach-Eya transcriptional effects in mammalian organogenesis. Nature 426:247–254. https://doi.org/10.1038/nature02083

Ling C, Zheng Y, Yin F, Yu J, Huang J, Hong Y, Wu S, Pan D (2010) The apical transmembrane protein Crumbs functions as a tumor suppressor that regulates Hippo signaling by binding to expanded. Proc Natl Acad Sci USA 107:10532–10537. https://doi.org/10.1073/pnas.1004279107

Liu C, Li Y, Peng M, Laties AM, Wen R (1999) Activation of caspase-3 in the retina of transgenic rats with the rhodopsin mutation s334ter during photoreceptor degeneration. J Neurosci 19:4778–4785

Lotery AJ, Jacobson SG, Fishman GA, Weleber RG, Fulton AB, Namperumalsamy P, Heon E, Levin AV, Grover S, Rosenow JR, Kopp KK, Sheffield VC, Stone EM (2001) Mutations in the CRB1 gene cause Leber congenital amaurosis. Arch Ophthalmol 119:415–420

Mao H, James T, Schwein A, Shabashvili AE, Hauswirth WW, Gorbatyuk MS, Lewin AS (2011) AAV delivery of wild-type rhodopsin preserves retinal function in a mouse model of autosomal dominant retinitis pigmentosa. Hum Gene Ther 22:567–575. https://doi.org/10.1089/hum.2010.140

Mardon G, Solomon NM, Rubin GM (1994) dachshund encodes a nuclear protein required for normal eye and leg development in Drosophila. Development (Camb Engl) 120:3473–3486

Masai I, Okazakit A, Hosoyat T, Hottatt Y (1993) Drosophila retinal degeneration A gene encodes an eye-specific diacylglycerol kinase with cysteine-rich zinc-finger motifs and ankyrin repeats (signal transduction/phosphatidylinositol metabolism). Neurobiology 90:11157–11161. https://doi.org/10.1073/pnas.90.23.11157

Masai I, Stemple DL, Okamoto H, Wilson SW (2000) Midline signals regulate retinal neurogenesis in zebrafish. Neuron 27:251–263

Maw MA, Corbeil D, Koch J, Hellwig A, Wilson-Wheeler JC, Bridges RJ, Kumaramanickavel G, John S, Nancarrow D, Röper K, Weigmann A, Huttner WB, Denton MJ (2000) A frameshift mutation in prominin (mouse)-like 1 causes human retinal degeneration. Human molecular genetics 9:27–34. https://doi.org/10.1093/Hmg/9.1.27 doi

McKay GJ, Clarke S, Davis JA, Simpson DAC, Silvestri G (2005) Pigmented paravenous chorioretinal atrophy is associated with a mutation within the crumbs homolog 1 (CRB1) gene. Investigative Ophthalmol Vis Sci 46:322–328. https://doi.org/10.1167/iovs.04-0734

Meyertholen EP, Stein PJ, Williams MA, Ostroy SE (1987) Studies of the *Drosophila* norpA phototransduction mutant. J Comparative Physiol A 161:793–798. https://doi.org/10.1007/BF00610221

Michno K, van de Hoef D, Wu H, Boulianne GL (2005) Modeling age-related diseases in Drosophila: can this fly? Curr Top Dev Biol 71:199–223. https://doi.org/10.1016/s0070-2153(05)71006-1

Myers EW, Sutton GG, Delcher AL, Dew IM, Fasulo DP, Flanigan MJ, Kravitz SA, Mobarry CM, Reinert KH, Remington KA, Anson EL, Bolanos RA, Chou HH, Jordan CM, Halpern AL, Lonardi S, Beasley EM, Brandon RC, Chen L, Dunn PJ, Lai Z, Liang Y, Nusskern DR, Zhan M, Zhang Q, Zheng X, Rubin GM, Adams MD, Venter JC (2000) A whole-genome assembly of Drosophila. Science 287:2196–2204

Nathans J, Weitz CJ, Agarwal N, Nir I, Papermaster DS (1989) Production of bovine rhodopsin by mammalian cell lines expressing cloned cDNA: spectrophotometry and subcellular localization. Vision Res 29:907–914

Neumann CJ, Nuesslein-Volhard C (2000) Patterning of the zebrafish retina by a wave of sonic hedgehog activity. Science 289:2137–2139

Nie J, Mahato S, Mustill W, Tipping C, Bhattacharya SS, Zelhof AC (2012) Cross species analysis of prominin reveals a conserved cellular role in invertebrate and vertebrate photoreceptor cells. Dev Biol 371:312–320. https://doi.org/10.1016/j.ydbio.2012.08.024

Niimi T, Seimiya M, Kloter U, Flister S, Gehring WJ (1999) Direct regulatory interaction of the eyeless protein with an eye-specific enhancer in the sine oculis gene during eye induction in Drosophila. Dev (Camb Engl) 126:2253–2260

Orem NR, Dolph PJ (2002) Loss of the phospholipase C gene product induces massive endocytosis of rhodopsin and arrestin in Drosophila photoreceptors. Vision Res 42:497–505. https://doi.org/10.1016/S0042-6989(01)00229-2

Orrenius S, Zhivotovsky B, Nicotera P (2003) Regulation of cell death: the calcium-apoptosis link. Nat Rev Mol Cell Biol 4:552–565. https://doi.org/10.1038/nrm1150

Ostrin EJ (2006) Genome-wide identification of direct targetsof the Drosophila retinal determination protein Eyeless. Genome Res 16:466–476. https://doi.org/10.1101/gr.4673006

Papatsenko D, Nazina A, Desplan C (2001) A conserved regulatory element present in all Drosophila rhodopsin genes mediates Pax6 functions and participates in the fine-tuning of cell-specific expression. Mech Dev 101:143–153. https://doi.org/10.1016/S0925-4773(00)00581-5

Papayannopoulos V, Tomlinson A, Panin VM, Rauskolb C, Irvine KD (1998) Dorsal-ventral signaling in the Drosophila eye. Science 281:2031–2034

Pappu KS (2005) Dual regulation and redundant function of two eye-specific enhancers of the Drosophila retinal determination gene dachshund. Development 132:2895–2905. https://doi.org/10.1242/dev.01869

Patterson JT, Muller HJ (1930) Are "Progressive" mutations produced by X-rays? Genetics 15:495–577

Pellikka M, Tanentzapf M, Pinto M, Smith C, McGlade CJ, Ready DF, Tepass U (2002) Crumbs, the Drosophila homologue of human CRB1/RP12, is essential for photoreceptor morhogenesis. Nature 416:143–149

Peng GH, Ahmad O, Ahmad F, Liu J, Chen S (2005) The photoreceptor-specific nuclear receptor Nr2e3 interacts with Crx and exerts opposing effects on the transcription of rod versus cone genes. Hum Mol Genet 14:747–764. https://doi.org/10.1093/hmg/ddi070

Pepple KL, Atkins M, Venken K, Wellnitz K, Harding M, Frankfort B, Mardon G (2008) Two-step selection of a single R8 photoreceptor: a bistable loop between senseless and rough locks in R8 fate. Development 135:4071–4079. https://doi.org/10.1242/dev.028951

Pichaud F, Casares F (2000) homothorax and iroquois-C genes are required for the establishment of territories within the developing eye disc. Mech Dev 96:15–25

Pignoni F, Hu B, Zavitz KH, Xiao J, Garrity PA, Zipursky SL (1997) The eye-specification proteins So and Eya form a complex and regulate multiple steps in Drosophila eye development. Cell 91:881–891. https://doi.org/10.1016/S0092-8674(00)80480-8

Pocha SM, Shevchenko A, Knust E (2011) Crumbs regulates rhodopsin transport by interacting with and stabilizing myosin V. J Cell Biol 195:827–838. https://doi.org/10.1083/jcb.201105144

Posnien N, Hopfen C, Hilbrant M, Ramos-Womack M, Murat S, Schonauer A, Herbert SL, Nunes MD, Arif S, Breuker CJ, Schlotterer C, Mitteroecker P, McGregor AP (2012) Evolution of eye morphology and rhodopsin expression in the Drosophila melanogaster species subgroup. PLoS One 7:e37346. https://doi.org/10.1371/journal.pone.0037346

Punzo C (2004) Functional divergence between eyeless and twin of eyeless in Drosophila melanogaster. Development 131:3943–3953. https://doi.org/10.1242/dev.01278

Punzo C, Kurata S, Gehring WJ (2001) The eyeless homeodomain is dispensable for eye development in Drosophila. Genes Dev 15:1716–1723. https://doi.org/10.1101/gad.196401

Quiring R, Walldorf U, Kloter U, Gehring W (1994) Homology of the eyeless gene of Drosophila to the small eye gene in mice and aniridia in humans. Science 265:785–789. https://doi.org/10.1126/science.7914031

Ragge NK, Brown AG, Poloschek CM, Lorenz B, Henderson RA, Clarke MP, Russell-Eggitt I, Fielder A, Gerrelli D, Martinez-Barbera JP, Ruddle P, Hurst J, Collin JR, Salt A, Cooper ST, Thompson PJ, Sisodiya SM, Williamson KA, Fitzpatrick DR, van Heyningen V, Hanson IM (2005) Heterozygous mutations of OTX2 cause severe ocular malformations. Am J Hum Genet 76:1008–1022. https://doi.org/10.1086/430721

Raghu P, Usher K, Jonas S, Chyb S, Polyanovsky A, Hardie RC (2000) Constitutive activity of the light-sensitive channels TRP and TRPL in the Drosophila diacylglycerol kinase mutant. rdgA Neuron 26:169–179. https://doi.org/10.1016/S0896-6273(00)81147-2

Raymond PA, Barthel LK (2004) A moving wave patterns the cone photoreceptor mosaic array in the zebrafish retina. Int J Dev Biol 48:935–945. https://doi.org/10.1387/ijdb.041873pr

Reiter LT, Potocki L, Chien S, Gribskov M, Bier E (2001) A systematic analysis of human disease-associated gene sequences in Drosophila melanogaster. Genome Res 11:1114–1125. https://doi.org/10.1101/gr.169101

Renfranz PJ, Benzer S (1989) Monoclonal antibody probes discriminate early and late mutant defects in development of the Drosophila retina. Dev Biol 136:411–429

Richard M, Grawe F, Knust E (2006) DPATJ plays a role in retinal morphogenesis and protects against light-dependent degeneration of photoreceptor cells in the Drosophila eye. Dev Dyn 235:895–907. https://doi.org/10.1002/dvdy.20595

Roessler E, Belloni E, Gaudenz K, Jay P, Berta P, Scherer SW, Tsui LC, Muenke M (1996) Mutations in the human sonic hedgehog gene cause holoprosencephaly. Nat Genet 14:357–360. https://doi.org/10.1038/ng1196-357

Rosenbaum EE, Hardie RC, Colley NJ (2006) Calnexin is essential for rhodopsin maturation, Ca^{2+} regulation, and photoreceptor cell survival. Neuron 49:229–241. https://doi.org/10.1016/j.neuron.2005.12.011

Rosenbaum EE, Brehm KS, Vasiljevic E, Liu CH, Hardie RC, Colley NJ (2011) XPORT-Dependent transport of TRP and rhodopsin. Neuron 72:602–615. https://doi.org/10.1016/j.neuron.2011.09.016

Rubin GM, Lewis EB (2000) A brief history of Drosophila's contributions to genome research. Science 287:2216–2218

Salam AA, Hafner FM, Linder TE, Spillmann T, Schinzel AA, Leal SM (2000) A novel locus (DFNA23) for prelingual autosomal dominant nonsyndromic hearing loss maps to 14q21-q22 in a swiss German kindred. Am J Hum Genet 66:1984–1988. https://doi.org/10.1086/302931

Salzer CL, Kumar JP (2009) Position dependent responses to discontinuities in the retinal determination network. Dev Biol 326:121–130. https://doi.org/10.1016/j.ydbio.2008.10.048

Sanes JR, Zipursky SL (2010) Design principles of insect and vertebrate visual systems. Neuron 66:15–36. https://doi.org/10.1016/j.neuron.2010.01.018

Sanyanusin P, Schimmenti LA, McNoe LA, Ward TA, Pierpont ME, Sullivan MJ, Dobyns WB, Eccles MR (1995) Mutation of the PAX2 gene in a family with optic nerve colobomas, renal anomalies and vesicoureteral reflux. Nat Genet 9:358–364. https://doi.org/10.1038/ng0495-358

Sarkar PS, Appukuttan B, Han J, Ito Y, Ai C, Tsai W, Chai Y, Stout JT, Reddy S (2000) Heterozygous loss of Six5 in mice is sufficient to cause ocular cataracts. Nat Genet 25:110–114. https://doi.org/10.1038/75500

Sen A, Cox RT (2017) Fly Models of human diseases: Drosophila as a model for understanding human mitochondrial mutations and disease. Curr Top Dev Biol 121:1–27. https://doi.org/10.1016/bs.ctdb.2016.07.001

Senturk M, Bellen HJ (2017) Genetic strategies to tackle neurological diseases in fruit flies. Curr Opin Neurobiol 50:24–32. https://doi.org/10.1016/j.conb.2017.10.017

Shen W, Mardon G (1997) Ectopic eye development in Drosophila induced by directed dachshund expression. Dev (Camb Engl) 124:45–52

Sheng G, Thouvenot E, Schmucker D, Wilson DS, Desplan C (1997) Direct regulation of rhodopsin 1 by Pax-6/eyeless in Drosophila: evidence for a conserved function in photoreceptors. Genes Dev 11:1122–1131. https://doi.org/10.1101/gad.11.9.1122

Shokravi MT, Dryja TP (1993) Retinitis pigmentosa and the rhodopsin gene. Int Ophthalmol Clin 33:219–228

Skalicky SE, White AJ, Grigg JR, Martin F, Smith J, Jones M, Donaldson C, Smith JE, Flaherty M, Jamieson RV (2013) Microphthalmia, anophthalmia, and coloboma and associated ocular and systemic features: understanding the spectrum. JAMA Ophthalmol 131:1517–1524. https://doi.org/10.1001/jamaophthalmol.2013.5305

Sobreira N, Schiettecatte F, Boehm C, Valle D, Hamosh A (2015a) New tools for Mendelian disease gene identification: PhenoDB variant analysis module; and GeneMatcher, a web-based tool for linking investigators with an interest in the same gene. Hum Mutat 36:425–431. https://doi.org/10.1002/humu.22769

Sobreira N, Schiettecatte F, Valle D, Hamosh A (2015b) GeneMatcher: a matching tool for connecting investigators with an interest in the same gene. Hum Mutat 36:928–930. https://doi.org/10.1002/humu.22844

Sohocki MM, Sullivan LS, Mintz-Hittner HA, Birch D, Heckenlively JR, Freund CL, McInnes RR, Daiger SP (1998) A range of clinical phenotypes associated with mutations in CRX, a photoreceptor transcription-factor gene. Am J Hum Genet 63:1307–1315. https://doi.org/10.1086/302101

Sonoshita M, Cagan RL (2017) Modeling human cancers in Drosophila. Curr Top Dev Biol 121:287–309. https://doi.org/10.1016/bs.ctdb.2016.07.008

Stark WS, Sapp R (1987) Ultrastructure of the retina of drosophila melanogaster. The mutant ora (outer rhabdomeres absent) and its inhibition of degeneration in rdgb (retinal degeneration-b). J Neurogenet 4:227–240. https://doi.org/10.3109/01677068709102343

Steele F, O'Tousa JE (1990) Rhodopsin activation causes retinal degeneration in drosophila rdgC mutant. Neuron 4:883–890. https://doi.org/10.1016/0896-6273(90)90141-2

Sun Y, Kanekar SL, Vetter ML, Gorski S, Jan YN, Glaser T, Brown NL (2003) Conserved and divergent functions of Drosophila atonal, amphibian, and mammalian Ath5 genes. Evol Dev 5:532–541

Sundaram K, Mani SK, Kitatani K, Wu K, Pestell RG, Reddy SV (2008) DACH1 negatively regulates the human RANK ligand gene expression in stromal/preosteoblast cells. J Cell Biochem 103:1747–1759. https://doi.org/10.1002/jcb.21561

Sung CH, Davenport CM, Nathans J (1993) Rhodopsin mutations responsible for autosomal dominant retinitis pigmentosa. Clustering of functional classes along the polypeptide chain. J Biol Chem 268:26645–26649

Tahayato A, Sonneville R, Pichaud F, Wernet MF, Papatsenko D, Beaufils P, Cook T, Desplan C (2003) Otd/Crx, a dual regulator for the specification of ommatidia subtypes in the Drosophila retina. Dev Cell 5:391–402

Terrell D, Xie B, Workman M, Mahato S, Zelhof A, Gebelein B, Cook T (2012) OTX2 and CRX rescue overlapping and photoreceptor-specific functions in the Drosophila eye. Dev Dyn 241:215–228. https://doi.org/10.1002/dvdy.22782

Ton CCT, Hirvonen H, Miwa H, Weil MM, Monaghan P, Jordan T, van Heyningen V, Hastie ND, Meijers-Heijboer H, Drechsler M, Royer-Pokora B, Collins F, Swaroop A, Strong LC, Saunders GF (1991) Positional cloning and characterization of a paired box- and homeobox-containing gene from the aniridia region. Cell 67:1059–1074. https://doi.org/10.1016/0092-8674(91)90284-6

Toy J, Norton JS, Jibodh SR, Adler R (2002) Effects of homeobox genes on the differentiation of photoreceptor and nonphotoreceptor neurons. Invest Ophthalmol Vis Sci 43:3522–3529

Treisman JE (1999) A conserved blueprint for the eye? BioEssays 21: 843–850. https://doi.org/10.1002/(SICI)1521-1878(199910)21:10%3C843::AID-BIES6%3E3.0.CO;2-J

Treisman JE (2013) Retinal differentiation in Drosophila. Wiley Interdiscip Rev Dev Biol 2:545–557. https://doi.org/10.1002/wdev.100

Verbakel SK, van Huet RAC, Boon CJF, den Hollander AI, Collin RWJ, Klaver CCW, Hoyng CB, Roepman R, Klevering BJ (2018) Non-syndromic retinitis pigmentosa. Prog Retin Eye Res 66:157–186. https://doi.org/10.1016/j.preteyeres.2018.03.005

Voolstra O, Oberhauser V, Sumser E, Meyer NE, Maguire ME, Huber A, Von Lintig J (2010) NinaB is essential for Drosophila vision but induces retinal degeneration in opsin-deficient photoreceptors. J Biol Chem 285:2130–2139. https://doi.org/10.1074/jbc.M109.056101

Vopalensky P, Kozmik Z (2009) Eye evolution: common use and independent recruitment of genetic components. Philos Trans R Soc Lond B Biol Sci 364:2819–2832. https://doi.org/10.1098/rstb.2009.0079

Wallis DE, Roessler E, Hehr U, Nanni L, Wiltshire T, Richieri-Costa A, Gillessen-Kaesbach G, Zackai EH, Rommens J, Muenke M (1999) Mutations in the homeodomain of the human SIX3 gene cause holoprosencephaly. Nat Genet 22:196–198. https://doi.org/10.1038/9718

Wang T, Montell C (2007) Phototransduction and retinal degeneration in Drosophila. Pflugers Archiv Euro J Physiol. 454:821–847. https://doi.org/10.1007/s00424-007-0251-1

Wang SZ, Adler R, Nathans J (1992) A visual pigment from chicken that resembles rhodopsin: amino acid sequence, gene structure, and functional expression. Biochemistry 31:3309–3315

Wang T, Xu H, Oberwinkler J, Gu Y, Hardie RC, Montell C (2005) Light activation, adaptation, and cell survival functions of the Na^+/Ca^{2+} exchanger CalX. Neuron 45:367–378. https://doi.org/10.1016/j.neuron.2004.12.046

Wang T, Lao U, Edgar BA (2009) TOR-mediated autophagy regulates cell death in Drosophila neurodegenerative disease. J Cell Biol 186:703–711. https://doi.org/10.1083/jcb.200904090

Wang X, Wang T, Jiao Y, von Lintig J, Montell C (2010) Requirement for an enzymatic visual cycle in Drosophila. Curr Biol 20:93–102. https://doi.org/10.1016/j.cub.2009.12.022

Wang X, Wang T, Ni JD, von Lintig J, Montell C (2012) The Drosophila visual cycle and de novo chromophore synthesis depends on rdhB. J Neurosci 32:3485–3491. https://doi.org/10.1523/jneurosci.5350-11.2012

Wangler MF, Yamamoto S, Bellen HJ (2015) Fruit flies in biomedical research. Genetics 199:639–653. https://doi.org/10.1534/genetics.114.171785

Wangler MF, Yamamoto S, Chao HT, Posey JE, Westerfield M, Postlethwait J, Hieter P, Boycott KM, Campeau PM, Bellen HJ (2017) Model organisms facilitate rare disease diagnosis and therapeutic research. Genetics 207:9–27. https://doi.org/10.1534/genetics.117.203067

Warburg M (1993) Classification of microphthalmos and coloboma. J Med Genet 30:664–669

Wawersik S, Maas RL (2000) Vertebrate eye development as modeled in Drosophila. Hum Mol Genet 9:917–925

Weasner B, Salzer C, Kumar JP (2007) Sine oculis, a member of the SIX family of transcription factors, directs eye formation. Dev Biol 303:756–771. https://doi.org/10.1016/j.ydbio.2006.10.040

Weinberger S, Topping MP, Yan J, Claeys A, Geest N, Ozbay D, Hassan T, He X, Albert JT, Hassan BA, Ramaekers A (2017) Evolutionary changes in transcription factor coding sequence quantitatively alter sensory organ development and function. Elife 6:e26402. https://doi.org/10.7554/eLife.26402

Wernet MF, Mazzoni EO, Celik A, Duncan DM, Duncan I, Desplan C (2006) Stochastic spineless expression creates the retinal mosaic for colour vision. Nature 440:174–180. https://doi.org/10.1038/nature04615

Williamson KA, FitzPatrick DR (2014) The genetic architecture of microphthalmia, anophthalmia and coloboma. Eur J Med Genet 57:369–380. https://doi.org/10.1016/j.ejmg.2014.05.002

Wu K, Yang Y, Wang C, Davoli MA, D'Amico M, Li A, Cveklova K, Kozmik Z, Lisanti MP, Russell RG, Cvekl A, Pestell RG (2003) DACH1 inhibits transforming growth factor-β signaling through binding Smad4. J Biol Chem 278:51673–51684. https://doi.org/10.1074/jbc.M310021200

Wu K, Li A, Rao M, Liu M, Dailey V, Yang Y, Di Vizio D, Wang C, Lisanti MP, Sauter G, Russell RG, Cvekl A, Pestell RG (2006) DACH1 Is a cell fate determination factor that inhibits cyclin D1 and breast tumor growth. Mol Cell Biol 26:7116–7129. https://doi.org/10.1128/MCB.00268-06

Wu K, Katiyar S, Li A, Liu M, Ju X, Popov VM, Jiao X, Lisanti MP, Casola A, Pestell RG (2008) Dachshund inhibits oncogene-induced breast cancer cellular migration and invasion through suppression of interleukin-8. Proc Natl Acad Sci USA 105:6924–6929. https://doi.org/10.1073/pnas.0802085105

Wu K, Katiyar S, Witkiewlcz A, Li A, Mccue P, Song LN, Tian L, Jin M, Pestell RG (2009) The cell fate Determination factor Dachshund inhibits androgen receptor signaling and prostate cancer cellular growth. Can Res 69:3347–3355. https://doi.org/10.1158/0008-5472.CAN-08-3821

Wu K, Jiao X, Li Z, Katiyar S, Casimiro MC, Yang W, Zhang Q, Willmarth NE, Chepelev I, Crosariol M, Wei Z, Hu J, Zhao K, Pestell RG (2011) Cell fate determination factor Dachshund reprograms breast cancer stem cell function. J Biol Chem 286:2132–2142. https://doi.org/10.1074/jbc.M110.148395

Xiong B, Bellen HJ (2013) Rhodopsin homeostasis and retinal degeneration: lessons from the fly. Trends Neurosci 36:652–660. https://doi.org/10.1016/j.tins.2013.08.003

Xu PX, Zhang X, Heaney S, Yoon A, Michelson AM, Maas RL (1999) Regulation of Pax6 expression is conserved between mice and flies. Dev (Camb Engl) 126:383–395

Xu Q, Wang Y, Dabdoub A, Smallwood PM, Williams J, Woods C, Kelley MW, Jiang L, Tasman W, Zhang K, Nathans J (2004) Vascular development in the retina and inner ear: control by Norrin and Frizzled-4, a high-affinity ligand-receptor pair. Cell 116:883–895

Yamamoto S, Jaiswal M, Charng WL, Gambin T, Karaca E, Mirzaa G, Wiszniewski W, Sandoval H, Haelterman NA, Xiong B, Zhang K, Bayat V, David G, Li T, Chen K, Gala U, Harel T, Pehlivan D, Penney S, Vissers L, de Ligt J, Jhangiani SN, Xie Y, Tsang SH, Parman Y, Sivaci M, Battaloglu E, Muzny D, Wan YW, Liu Z, Lin-Moore AT, Clark RD, Curry CJ, Link N, Schulze KL, Boerwinkle E, Dobyns WB, Allikmets R, Gibbs RA, Chen R, Lupski JR, Wangler MF, Bellen HJ (2014) A Drosophila genetic resource of mutants to study mechanisms underlying human genetic diseases. Cell 159:200–214. https://doi.org/10.1016/j.cell.2014.09.002

Yan J, Anderson C, Viets K, Tran S, Goldberg G, Small S, Johnston RJ Jr (2017) Regulatory logic driving stable levels of defective proventriculus expression during terminal photoreceptor specification in flies. Development 144:844–855. https://doi.org/10.1242/dev.144030

Yao JG, Sun YH (2005) Eyg and Ey Pax proteins act by distinct transcriptional mechanisms in Drosophila development. EMBO J 24:2602–2612. https://doi.org/10.1038/sj.emboj.7600725

Yariz KO, Sakalar YB, Jin X, Hertz J, Sener EF, Akay H, Ozbek MN, Farooq A, Goldberg J, Tekin M (2015) A homozygous SIX6 mutation is associated with optic disc anomalies and macular atrophy and reduces retinal ganglion cell differentiation. Clin Genet 87:192–195. https://doi.org/10.1111/cge.12374

Yoon J, Ben-Ami HC, Hong YS, Park S, Strong LL, Bowman J, Geng C, Baek K, Minke B, Pak WL (2000) Novel mechanism of massive photoreceptor degeneration caused by mutations in the trp gene of Drosophila. J Neurosci 20:649–659

Younossi-Hartenstein A, Tepass U, Hartenstein V (1993) Embryonic origin of the imaginal discs of the head of Drosophila melanogaster. Roux Arch Dev Biol 203:60–73. https://doi.org/10.1007/bf00539891

Yu M, Liu Y, Li J, Natale BN, Cao S, Wang D, Amack JD, Hu H (2016) Eyes shut homolog is required for maintaining the ciliary pocket and survival of photoreceptors in zebrafish. Biol Open 5:1662–1673. https://doi.org/10.1242/bio.021584

Yu W, Mookherjee S, Chaitankar V, Hiriyanna S, Kim JW, Brooks M, Ataeijannati Y, Sun X, Dong L, Li T, Swaroop A, Wu Z (2017) Nrl knockdown by AAV-delivered CRISPR/Cas9 prevents retinal degeneration in mice. Nat Commun 8:1–15. https://doi.org/10.1038/ncomms14716

Zelhof AC, Hardy RW, Becker A, Zuker CS (2006) Transforming the architecture of compound eyes. Nature 443:696–699. https://doi.org/10.1038/nature05128

Zhang T, Ranade S, Cai CQ, Clouser C, Pignoni F (2006) Direct control of neurogenesis by selector factors in the fly eye: regulation of atonal by Ey and So. Development 133:4881–4889. https://doi.org/10.1242/dev.02669

Zhao F, Wang M, Li S, Bai X, Bi H, Liu Y, Ao X, Jia Z, Wu H (2015) DACH1 inhibits SNAI1-mediated epithelial-mesenchymal transition and represses breast carcinoma metastasis. Oncogenesis 4:1–14. https://doi.org/10.1038/oncsis.2015.3

Zhou Q, Zhang T, Jemc JC, Chen Y, Chen R, Rebay I, Pignoni F (2014) Onset of atonal expression in Drosophila retinal progenitors involves redundant and synergistic contributions of Ey/Pax6 and So binding sites within two distant enhancers. Dev Biol 386:152–164. https://doi.org/10.1016/j.ydbio.2013.11.012

Zhu H, Owen MR, Mao Y (2016) The spatiotemporal order of signaling events unveils the logic of development signaling. Bioinformatics 32:2313–2320. https://doi.org/10.1093/bioinformatics/btw121

Zuber ME (2003) Specification of the vertebrate eye by a network of eye field transcription factors. Development 130:5155–5167. https://doi.org/10.1242/dev.00723