**Mouse models for microphthalmia, anophthalmia and cataracts**

Jochen Graw

Helmholtz Center Munich; Institute of Developmental Genetics, Neuherberg, Germany

**Corresponding address:**

Prof. Dr. Jochen Graw

ORCID-ID: 0000-0003-0298-9660

Institute of Developmental Genetics,

Helmholtz Center Munich, German Research Center for Environmental Health,

Ingolstädter Landstrasse 1

D-85764 Neuherberg, Germany

Tel: ++49-89/3187-2610

Email: [graw@helmholtz-muenchen.de](mailto:graw@helmholtz-muenchen.de)

Abstract

Mouse mutants are a long lasting, valuable tool to identify genes underlying eye diseases, because absence of eyes, very small eyes and severely affected, cataractous eyes are easily to detect without major technical equipment. In mice, actually 145 genes or loci are known for anophthalmia, 269 for microphthalmia, and 180 for cataracts. Approximately, 25% of the loci are not yet characterized, however, some of the ancient lines are extinct and not available for future research. The phenotypes of the mutants represent a continuous spectrum either in anophthalmia and microphthalmia, or in microphthalmia and cataracts. On the other side, mouse models are still missing for some genes, which have been identified in human families to be causative for anophthalmia, microphthalmia, or cataracts. Finally, the mouse offers the possibility to genetically test the roles of modifiers and the role of SNPs – these aspects open new avenues for ophthalmogenetics in the mouse.

**Introduction**

Blindness in children is a very severe condition affecting ~14 mio children worldwide (Solebo et al., 2017). Among them, cataracts are the major subgroup affecting 28% of the cases (Solebo et al., 2017); the prevalence of congenital cataracts ranges from 0.32 to 22.9/10,000 children in different geographic regions over the world (Sheeladavi et al., 2016). Similarly, the prevalence of anopthalmia/microphthalmia has been estimated between 0.2–3.0 per 10,000 births (summarized by Llorente-González et al., 2011) with an incidence of congenital anophthalmia (in England) ranging from 0.4 to 2.9 per 100,000 infants and an incidence of congenital microphthalmia ranging from 10.0-10.8 per 100,000 children (Dharmasena et al., 2017). Although these eye disorders are rare, they are major challenges for the treating clinicians and for the families, who have to fight the diseases. Discussing the reasons for such severe disorders, we have to consider environmental factors like intrauterine infections or toxins, but also genetic reasons. Here, we will focus on these genetic aspects leading to anophthalmia, microphthalmia or congenital cataracts. Moreover, we will concentrate on mouse models, because the mouse is genetically the best characterized mammalian model system for hereditary diseases, particularly, if they affect the eye.

Anophthalmia, severe microphthalmia and strong cataracts are easily to detect by careful investigators, and therefore, it is not surprising that some of the first mouse mutants with severe eye defects were published in the first half of the 20th century (Little and Bagg, 1923; Hertwig, 1942). Later, several systematic screens were conducted using ionizing radiation or ethyl-nitroso urea (ENU) as mutagenic agents to identify disease-causing genes including genes leading to eye disorders (Kratochvilova 1981; Ehling et al., 1985; Hrabé de Angelis and Balling, 1998; Acevedo-Arozena et al., 2008; Clark et al., 2004; Aigner et al., 2011). These programs have been very successful in the identification of novel genes; today, ENU screens to detect novel genes are still performed at the Riken Center (Japan; http://www.riken.jp/en) and by the Bench-to-Bassinet program (b2b; www.benchtobassinet.com). On the other site, targeted and/or conditional mutagenesis are performed nowadays more frequently to better understand the underlying mechanisms during mammalian eye development. Another source for novel genes involved in early eye development are the mouse phenotyping centers, which systematically screen targeted knockout mutants for a broad variety of pathological phenotypes including the eye (http://www.mousephenotype.org/). The review here summarizes the genetic characterizations of mouse mutants suffering from microphthalmia, anophthalmia, and cataracts, which lead to a better understanding of eye development in mammals. New resources will be discussed to complete the mosaic.

**Anophthalmia**

Anophthalmia is the most severe phenotype, which might occur during eye development, since it indicates that eye development was stopped at a very early stage. The mammalian phenotype ontology annotation lists 145 genes being associated with anophthalmia (just 28 mutations are unknown). Some of them, *Rax*, *Sox2*, *Pax6*, *Lhx2* and two *Bmp* genes (*Bmp4* and *Bmp7*) are of particular interest.

One of the early anophthalmic mouse mutant was identified by Herman Chase (1944) and referred to as eyeless (gene symbol *ey*). It took almost 60 years, till the mutation was characterized: it is a point mutation affecting the ***Rax*** gene (retina and anterior neural fold homeobox); it changes the Met at pos. 10 to Leu (M10L) (Tucker et al., 2001). The *Raxey* allele is hypomorphic, since the homozygous mutants are fully viable; in contrast, the homozygous knockout mutants of *Rax* are perinatally lethal (Mathers et al., 1997). The reason could be the type of the mutation leading to a conservative exchange of a hydrophobic Met by a hydrophobic Leu, which also affects an alternative, but in-frame translational start site. The authors argue that the *Raxey* allele leads to a reduced translation, but not to a real null allele (Tucker et al., 2001).

Another important gene for mammalian eye development is ***Sox2*** [SRY (sex determining region Y)-box 2]. Mutations in human *SOX2* lead to anophthalmia, but most mutations are *de-novo* mutations, which appeared in the parental germline, and most of the affected persons are sterile (Fantes et al., 2003; Ragge et al., 2005; Bakrania et al., 2007). Therefore, it is not surprising that no spontaneous mouse mutant of this gene exist. On the other hand, several targeted mouse mutants are available: most of them act as hypomorphic alleles (*Sox2LP*, *Sox2IR*, *Sox2EGFP*/IR and *Sox2EGFP*/LP) and show a range of eye phenotypes from mild microphthalmia to severe anophthalmia (Taranova et al., 2006).

The classical paradigm for anophthalmia in the mouse, however, are the homozygous ***Pax6*** mutants (paired box 6), which do not develop an eye in homozygous mutants (Fig. 1). The first mouse mutant suffering from a *Pax6* mutation was detected as a dominant homozygous lethal mutation with a “small-eye” phenotype as heterozygotes (gene symbol *Sey*; Roberts, 1967); the homozygous *Sey* mutants die perinatally. Another small-eye phenotype was found in 1975 at Harwell (UK) among offspring whose parents (fathers) have been treated by irradiation. Both mutations, *Sey* and *SeyH* (for Harwell) were mapped to mouse chromosome 2 and shown to be allelic (Hogan et al., 1986). Finally, the *Sey*-mutation was identified as a G🡪T transversion in codon 194 of the *Pax6* gene changing the corresponding position in the protein from a Gly to a stop codon, which results in a premature termination before the homeobox domain. The *SeyH* allele was characterized by a major deletion affecting not only *Pax6*, but also some adjacent genes (Hill et al., 1991). In the meantime, the MGI database lists 17 alleles of the mouse *Pax6* genes including a homozygous and hemizygous viable and fertile hypomorph allele (Favor et al., 2008). This allelic series of different phenotypes indicates the need to investigate more than just a knockout of a given gene to see the full spectrum, of which mutations in a given gene might be responsible for – to model also the variability in human genetics.

*Pax6* is the vertebrate homolog of the eyeless gene (*ey*) in *Drosophila*. Since the mouse *Pax6* gene is able to ectopically express a compound eye at the antennae of *Drosophila*, the dogma of different routes in evolution for a vertebrate eye vs those in *Drosophila* was skipped at least for the underlying genetic regulation (Halder et al., 1995).

**Microphthalmia**

Microphthalmia or small eyes seem to be a more frequent, but also a rather variable phenotype in the mouse. The mammalian phenotype ontology annotations in the mouse Genome database (mgi) contain 505 genotypes of 269 genes, 64 of them are unknown. There are significant overlaps with anophthalmia (e.g. mutation in *Pax6*, *Bmp4*, *Bmp7*) as well as with cataracts (e.g. mutations affecting genes coding for crystallins or connexins).

One of the early mouse mutants suffering from microphthalmia (gene symbol *mi*) was found by Paula Hertwig (1942) in a mouse cohort originating from irradiated mice; this particular mutation, however, most likely occurred spontaneously in the cohort (Arnheiter, 2010). Today, we know that this mutation affects the ***Mitf*** gene coding for the **microphthalmia-associated transcription factor** (today, it is also referred to as melanogenesis-associated transcription factor). The *mi* mutation is characterized by the loss of an Arg residue at the C-terminal part of the DNA-binding domain (Hodgkinson et al., 1993). In the meantime, many alleles of *Mitf* have been described in the mouse, and the phenotypic range of the mutations is very broad - from dominant phenotypes as in the *Mi* allele to recessive phenotypes with almost no pathological effect (as in the spotted allele). However, the microphthalmia phenotype occurs mainly in the homozygous mutants; since this transcription factor is expressed in many tissues and cell types including melanocytes, it affects also the skin or hair color. An excellent overview about this allelic series of the different mutations in the *Mitf* gene was published by Steingrimsson et al. (2004); it is a powerful example of the broad variability of disease-causing variations in a given gene.

Mutations in another gene coding for a transcription factor lead also to interesting phenotypic features – not only for microphthalmia. It is ***Pitx3***, coding for the **paired-like homeodomain transcription factor 3** (Fig. 2). The first mutant line, in which this gene was affected, was reported as aphakia (gene symbol *ak*) – it is a spontaneous recessive mutation showing a severe microphthalmia in homozygous mutants (Varnum and Stevens, 1968). Later, it turned out that the phenotype was caused by two major deletions in the promotor region of the *Pitx3* gene leading eventually to a classical null allele (Semina et al., 2000; Rieger et al., 2001). This mutation stops lens development at the stage of the lens vesicle; it does not detach from the surface ectoderm (the future cornea) and is degraded rapidly. The empty space is filled by hyperproliferating retinal tissue (Semina et al., 2000). Another allele of the mouse *Pitx3* gene is an insertion of a G after cDNA position 416 (416insG; exon 4). The shifted open reading frame is predicted to result in a hybrid protein still containing the PITX3 homeobox, but followed by 121 new amino acids. Since *Pitx3* is also expressed in the *substantia* *nigra* of the brain, this mutation affects also the formation of dopaminergic neurons in the *substantia nigra* – *Pitx3* mouse mutant lines are therefore an excellent model for Parkinson’s disease (Rosemann et al., 2010). Moreover, it turned out in later experiments that one of the target genes being regulated by PITX3 is *Foxe3*. The phenotype of a spontaneous *Foxe3* mutation, dysgenic lens (gene symbol *dyl*), resembles very much the *ak* phenotype, which can be easily explained by this interaction (Ahmad et al., 2013). However, it has to be noticed that the mouse phenotype of *Pitx3* mutations is quite different from the human situation, in which dominant anterior-segment dysgenesis and cataracts are the predominant phenotypes of *PITX3* mutations.

There is a further group of mouse mutants, which are characterized by similar types of **blebs** in combination with microphthalmia: blebbed (*bl*; Phillips, 1970), head blebs (*heb*; Varnum and Vox, 1981), eye blebs (*eb*;Chapman 1963), myelencephalic blebs (*my*; Little and Bagg 1923), and fetal hematoma (*fh*;Center, 1965); unfortunately, the *fh* mutant line became extinct before it could be molecularly characterized. The other four mutant lines carry mutations in genes coding for extracellular matrix proteins. The first one, *bl*, was identified in an F3 screen of a radiation genetics experiment and characterized by reduced eyes and clubbed feet. Later on, the reduced eyes were characterized as cryptophthalmos (fusion of eyelids), associated with distal limb defects. Finally, it turned out that the underlying mutation affects the *Fras1* gene (Fraser extracellular matrix complex subunit 1). The underlying mutation in the *bl*/*bl* mice was characterized as a nonsense mutation (7313C🡪A; S2200X) within the 47th exon of the *Fras1* gene (McGregor 2003). The *Fras1* gene is expressed in many organs; its expression in the lens seems to be causative for the eye malformation in the *bl* mutant line. The *my* mutant line arose in a radiation genetics experiment (Little and Bagg 1923) and exhibits a similar phenotype like *bl* (cryptophthalmos, and distal limb defects). By a series of genetic testing, this mutation was eventually mapped to *Frem2* (Fras1-related extracellular matrix protein 2), however, without showing the causative mutation in this particular gene (Jadeja et al., 2005). The *eb* mutants show also a recessive mode of inheritance and a similar phenotype like the *my* mutants (Chapman 1963). Takamiya et al. (2004) demonstrated that a deletion of exons 10 and 11 of the *Grip1* gene (glutamate receptor interacting protein 1) is responsible for the eye-blebs phenotype. The 4th mutant line of this series was *heb*, which is characterized by absent or malformed eyes; cryptophthalmos is always present in these mutants. The mutation in this particular line affects the gene *Frem1* encoding the Fras1-related extracellular matrix protein 1. The causative mutation is a LINE1 insertion 41 bp from the end of exon 17 (Smyth et al., 2004). In an ENU-induced mutation of similar phenotype (*bat*), these authors identified another causative mutation of the *Frem1* gene, close to the splice donor site of intron 25 leading to skipping of exon 25, a frame shift and a premature stop codon in exon 26. These mutant lines demonstrate the genetic heterogeneity of this phenotype, but they are now also considered being excellent models for the human Fraser syndrome, which is characterized as “cryptophthalmos with syndactyly” (Ramsing et al., 1990).

**Cataract**

Cataract mutants in the mouse are easily to detect, either by the naked eye, if the lens opacity is total and severe, or by a slit lamp, which is a routine, non-invasive device in ophthalmology and since decades also applied in mouse ophthalmogenetics (Kratochvilova 1981). Therefore, the mammalian phenotype ontology annotations count a similar high number of cataract genotypes like for microphthalmia, namely 459 genotypes. Among them, there are 138 genes listed with targeted mutations, 54 genes with point mutations or small InDels (partically overlapping) and 50 loci with unknown mutations.

Before the onset of major genetic screens for eye diseases, there were some spontaneous cataract mutants reported. Dominant cataracts were the Fraser Cataract (*CatFr*; Fraser and Schabtach, 1962), eye lens obsolescence (*Elo*; Oda et al., 1980), lens opacity (*Lop*; Lyon et al., 1981) or the Philly cataract (*Phil*, Kador et al., 1980). Among the recessive cataracts, the Nakano cataract (*nct*; Fukui et al., 1976) and the vacuolated lens (*vl*; Dickie et al., 1967) were well known. Among them, the Philly cataract was the first, which was characterized at a molecular level: the mutation is a 12 bp-deletion at the beginning of the 6th exon of the *Crybb2* gene (coding for βB2-crystallin).

The **crystallins** are highly concentrated and densely packed structural proteins in the eye lens; they are necessary for lens transparency. In mammals, we know two major crystallin families: the α-crystallin/small heat-shock protein family (consisting of 2 genes, *Cryaa* and *Cryab*), and the β/γ-crystallin “super”family (consisting of 8 *Cryg* genes and 6 *Cryb* genes). Mutations in each of these genes lead to several forms of cataract, however, there is no genotype-phenotype correlation possible beside the association between the onset of the crystallin expression in the lens and the age of onset of the disease: cataracts caused by mutations in *Cryg* genes are visible at weaning (for a review see Graw 2009), but mutations in the *Crybb2* gene lead to a progressive cataract starting a few weeks after birth (Kador et al., 1980, Ganguly et al., 2008). Mutations in the *Cryb*/*Cryg* genes, usually, lead to a dominant phenotype; however, *Cryaa* mutations may cause dominant (*Aey7*: c371T🡪A, Val124Glu; Graw et al., 2001) or recessive cataracts (*lop18*: c161G🡪A; Arg54His; Chang et al., 1999).

In the past, the different crystallin-encoding genes seemed to be expressed in the lens only, however, we learned during the last years that many of these genes have also other functions outside the lens. The mouse mutations in the *Cryab* gene showed not only cataracts, but also other diseases, affecting mainly the heart, but also skeletal muscle fibers (Andley et al., 2011). Similarly, the gene of the major β-crystallin, *Crybb2*, is expressed in the testes leading to subfertility if mutated (Duprey et al., 2007). *Crybb2* is also expressed in the brain (Magabo et al., 2000; Ganguly et al., 2008), and in homozygous *Crybb2* mutants, parvalbumin-positive interneurons as well as dendrites and dendritic branches in the hippocampus are decreased (Sun et al., 2013, 2018), and eventually changes in Schizophrenia-related endophenotypes have been observed (Heermann et al., 2018).

Another major group of cataract mutations in the mouse affects the *Gja8* gene (gap junction α8) coding for **connexin50**, which is one of the components of lens gap junctions (besides connexin43 and connexin46; for review see Gong et al., 2007; Berthoud and Ngezahayo, 2017). Point mutations in the *Gja8* gene lead to early-onset, dominant cataracts, whereas the knockout of this gene has a milder phenotype; however, since also gap junctions are formed by different combinations of the three connexins at different regions of the lens, the types of cataracts formed are highly diverse (Gong et al., 2007).

Among the spontaneously arisen cataract mutants, the *CatFr* and *Lop* mutations have been shown to be allelic soon after their discovery. The molecular analyses revealed point mutations in the gene encoding the **major intrinsic protein** (*Mip*) of the lens (also known as aquaporin 0). The *CatFr* mutation was demonstrated to be the result of a transposon-induced splicing error that substitutes a long terminal repeat sequence for the carboxy-terminus of MIP. The *Lop* mutation is characterized as a c151G🡪C exchange leading to a non-conservative exchange, Ala51Pro (Shiels and Bassnett, 1996).

Besides structural proteins like crystallins or membrane proteins, oxidative stress and perturbation in lens glutathione homeostasis were frequently discussed being causative mechanisms for cataract formation (for reviews see Lou 2003; Fan et al. 2017). Along with this line, a mutation (c3816T🡪A) in the *Pxdn* gene encoding peroxidasin was characterized leading to a premature stop codon. Morphologically, the mutant mice suffer from congenital cataracts because of a disorganized lens matrix and ruptures of the lens capsule - lens cells are present in the anterior chamber as well as in the posterior vitreous body (Yan et al., 2014).

The **recessive cataract mutations**, *nct* and *vl*, have been characterized moleculary, too: The Nakano cataract (*nct*) is characterized by a mutation affecting the *Cpox* gene encoding the coproporphyrinogen oxidase (Mori et al., 2013). The mutation *vl* was eventually characterized by an 8-bp deletion affecting the gene *Gpr161* coding for a G-coupled receptor (Matteson et al., 2007).

Cataractous lenses of the mouse are frequently reported to be smaller than wild-type lenses (e.g. Graw et al., 1990 a, b, Graw et al., 2004). Since the lens defines the size of the entire eye, also the entire eye is obviously smaller. Correspondingly, there is a group of mouse mutants, which are characterized as heterozygotes by a smaller size of the lens as determined by laser-interference biometry (Puk et al., 2006). At least some of these mutants develop cataracts later in life (e.g. mutation in *Cryba2*, encoding βA2-crystallin; Puk et al., 2011a) or in homozygotes [(e.g. mutation in *Lim2*, encoding the lens intrinsic membrane protein 2; Puk et al., 2011b, or a mutation in *Ercc2* (excision repair cross-complementing rodent repair deficiency, complementation group 2); Kunze et al., 2015; Fig. 3]. Therefore, it would be an interesting question, whether a reduced lens size is an early biomarker for cataract formation at later stages in life. Mouse mutants are a valuable tool to test this hypothesis.

# In addition to mouse models for congenital, childhood or juvenile cataracts, a few mutant lines exist also for senile cataracts. One group of such mutants is the senescent-accelerated mice (SAM) having been developed at the Kyoto university since 1970 (Takeda et al., 1981). Two of the SAM-lines develop also cataracts (SAM1P, Nishimoto et al., 1993; SAM9P, Ashida et al., 1994). Unfortunately, the underlying mutation(s) have not yet described for these mutant lines. Similarly, the EMORY mouse is also well recognized as a genetic model for age-related cataracts (Kuck et al., 1981/1982). There were several interesting ultrastructural and biochemical data reported like recently regional changes of AQP0-dependent square array junction and gap junctions (Biswas et al., 2014), but also for this mutant line the underlying mutation for the dominant mode of inheritance (Kuck et al., 1981/1982) remains to be elaborated

**Missing mutants and unknown mutations**

Analyzing the Mouse Genome Informatics (MGI) database on mouse mutants (http://www.informatics.jax.org/) for genes involved in anophthalmia, microphthalmia and cataracts, it is obvious that a remarkable number of discovered and phenotypically described mutants is not yet characterized at the molecular level (Tab. 1). Unfortunately, some of the older mouse lines are already extinct, but others are still available. Using the advanced sequencing techniques including whole exome sequencing, a solution of the remaining “old” mutant lines should be possible fast.

On the other side, comparing the numbers of genes identified in the mouse for eye diseases discussed here with the genes affected in humans, the number of mouse genes is much lower. For cataracts, the CatMap (<https://cat-map.wustl.edu/>) lists 324 cataract genes in humans, but the corresponding list of the mouse comprises just the half – or: 50% of the human cataract genes still need a mouse model! Unfortunately, no similar databases exist for genes involved in human anophthalmia or microphthalmia. The modern CRISPR/Cas9 technology (Knowlton and Smith 2017) offers one efficient possibility for designing new mutant alleles for interesting disease-causing mutations. Another option would be searching an archive of mouse mutations induced by ENU (e.g. <https://www.helmholtz-muenchen.de/ieg/services/scientific-resources/index.html>), re-deriving the mutants from frozen sperms and checking for the suggested phenotype.

Mouse mutant lines are today also systematically analyzed for their phenotypes (http://www.mousephenotype.org/). Worldwide, 18 institutions are collaborating in the International Mouse Phenotyping consortium (<http://www.mousephenotype.org/about-impc/impc-members>) screening also for eye anomalies. Results can be found on the IMPC website looking for “eye morphology”. However, there is no way to check directly for terms like anophthalmia, microphthalmia or cataract. Instead, mouse mutations can be found on the MGI database searching for diseases discussed in this review by using the corresponding gene-ontology terms (http://www.informatics.jax.org/vocab/gene\_ontology).

Finally, the mouse offers the possibility to genetically test the roles of modifiers and the role of SNPs – these aspects open new avenues for ophthalmogenetics in the mouse.

**Conclusions**

A wide range of mouse models for microphthalmia, anophthalmia and cataracts have been described in detail and molecularly characterized. However, for many mouse mutant lines the underlying mutation still needs to be identified. On the other side, for many genes, which have been shown to be involved in human families of anophthalmia, microphthalmia or cataracts, the corresponding mouse model still needs to be established.

**Acknowledgement**

I would like to thank Dr. Claudia Dalke for critical reading of the manuscript.

**References**

1. [Ahmad N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ahmad%20N%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Aslam M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aslam%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Muenster D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Muenster%20D%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Horsch M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Horsch%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Khan MA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Khan%20MA%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Carlsson P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Carlsson%20P%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Beckers J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Beckers%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24307298), [Graw J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Graw%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24307298): Pitx3 directly regulates *Foxe3* during early lens development. [Int J Dev Biol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=ahmad+n+2013+graw) 2013, 57:741-751.
2. Aigner B, Rathkolb B, Klempt M, Wagner S, Michel D, Klaften M, Laufs J, Schneider B, Sedlmeier R, Hrabé de Angelis M, Wolf E: [Generation of N-ethyl-N-nitrosourea-induced mouse mutants with deviations in hematological parameters.](https://www.ncbi.nlm.nih.gov/pubmed/21553221) Mamm Genome. 2011, 22:495-505
3. Andley UP, Hamilton PD, Ravi N, Weihl CC: [A knock-in mouse model for the R120G mutation of αB-crystallin recapitulates human hereditary myopathy and cataracts.](https://www.ncbi.nlm.nih.gov/pubmed/21445271) PLoS One, 2011, 6:e17671.
4. Arnheiter H: [The discovery of the microphthalmia locus and its gene, *Mitf*.](https://www.ncbi.nlm.nih.gov/pubmed/20807369) Pigment Cell Melanoma Res. 2010 (6):729-735.
5. Ashida Y, Takeda T, Hosokawa M: [Protein alterations in age-related cataract associated with a persistent hyaloid vascular system in senescence-accelerated mouse (SAM)](https://www.ncbi.nlm.nih.gov/pubmed/7859822). Exp Eye Res. 1994, 59:467-473.
6. Acevedo-Arozena A, Wells S, Potter P, Kelly M, Cox RD, Brown SD: [ENU mutagenesis, a way forward to understand gene function.](https://www.ncbi.nlm.nih.gov/pubmed/18949851) Annu Rev Genomics Hum Genet. 2008, 9:49-69
7. [Bakrania P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bakrania%20P%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Robinson DO](https://www.ncbi.nlm.nih.gov/pubmed/?term=Robinson%20DO%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Bunyan DJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bunyan%20DJ%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Salt A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Salt%20A%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Martin A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Martin%20A%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Crolla JA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Crolla%20JA%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Wyatt A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wyatt%20A%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Fielder A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fielder%20A%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Ainsworth J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ainsworth%20J%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Moore A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Moore%20A%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Read S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Read%20S%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Uddin J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Uddin%20J%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Laws D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Laws%20D%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Pascuel-Salcedo D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pascuel-Salcedo%20D%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Ayuso C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ayuso%20C%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Allen L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Allen%20L%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Collin JR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Collin%20JR%5BAuthor%5D&cauthor=true&cauthor_uid=17522144), [Ragge NK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ragge%20NK%5BAuthor%5D&cauthor=true&cauthor_uid=17522144): SOX2 anophthalmia syndrome: 12 new cases demonstrating broader phenotype and high frequency of large gene deletions. [Br J Ophthalmol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bakrania+p+2007) 2007, 91:1471-1476.
8. Berthoud VM, Ngezahayo A: [Focus on lens connexins.](https://www.ncbi.nlm.nih.gov/pubmed/28124626) BMC Cell Biol. 2017, 18(Suppl 1):6; doi: 10.1186/s12860-016-0116-6.
9. Biswas SK, Brako L, Gu S, Jiang JX, Lo WK: [Regional changes of AQP0-dependent square array junction and gap junction associated with cortical cataract formation in the Emory mutant mouse.](https://www.ncbi.nlm.nih.gov/pubmed/25088353) Exp Eye Res. 2014, 127:132-142
10. Center EM: fh - fetal hematoma. Mouse News Lett. 1965, 33:79-80
11. [Chang B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chang%20B%5BAuthor%5D&cauthor=true&cauthor_uid=10493778), [Hawes NL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hawes%20NL%5BAuthor%5D&cauthor=true&cauthor_uid=10493778), [Roderick TH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Roderick%20TH%5BAuthor%5D&cauthor=true&cauthor_uid=10493778), [Smith RS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20RS%5BAuthor%5D&cauthor=true&cauthor_uid=10493778), [Heckenlively JR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Heckenlively%20JR%5BAuthor%5D&cauthor=true&cauthor_uid=10493778), [Horwitz J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Horwitz%20J%5BAuthor%5D&cauthor=true&cauthor_uid=10493778), [Davisson MT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Davisson%20MT%5BAuthor%5D&cauthor=true&cauthor_uid=10493778): Identification of a missense mutation in the A-crystallin gene of the *lop18* mouse. Mol Vis. 1999, 5:21
12. Chapman DB; Hummel KP: Eye blebs (*eb*). Mouse News Lett. 1963, 28:32
13. Chase HB: Studies on an anophthalmic strain of mice. IV. A second major gene for anophthalmia. Genetics. 1944, 29:264-269
14. Clark AT, Goldowitz D, Takahashi JS, Vitaterna MH, Siepka SM, Peters LL, Frankel WN, Carlson GA, Rossant J, Nadeau JH, Justice MJ: [Implementing large-scale ENU mutagenesis screens in North America.](https://www.ncbi.nlm.nih.gov/pubmed/15619961) Genetica. 2004, 122:51-64
15. Dharmasena A, Keenan T, Goldacre R, Hall N, Goldacre MJ: [Trends over time in the incidence of congenital anophthalmia, microphthalmia and orbital malformation in England: database study.](https://www.ncbi.nlm.nih.gov/pubmed/27601422) Br J Ophthalmol. 2017, 101:735-739
16. Dickie MM, Vacuolated lens. Mouse News Lett. 1967, 36:39-40
17. [DuPrey KM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Duprey%20KM%5BAuthor%5D&cauthor=true&cauthor_uid=17392687), [Robinson KM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Robinson%20KM%5BAuthor%5D&cauthor=true&cauthor_uid=17392687), [Wang Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=17392687), [Taube JR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taube%20JR%5BAuthor%5D&cauthor=true&cauthor_uid=17392687), [Duncan MK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Duncan%20MK%5BAuthor%5D&cauthor=true&cauthor_uid=17392687): Subfertility in mice harboring a mutation in B2-crystallin. [Mol Vis.](https://www.ncbi.nlm.nih.gov/pubmed/?term=duprey+2007+crystallin) 2007, 13:366-373
18. Ehling UH, Charles DJ, Favor J, Graw J, Kratochvilova J, Neuhäuser-Klaus A, Pretsch W: [Induction of gene mutations in mice: the multiple endpoint approach.](https://www.ncbi.nlm.nih.gov/pubmed/4000165) Mutat Res. 1985, 150:393-401
19. Fan X, Monnier VM, Whitson J: [Lens glutathione homeostasis: Discrepancies and gaps in knowledge standing in the way of novel therapeutic approaches.](https://www.ncbi.nlm.nih.gov/pubmed/27373973) Exp Eye Res. 2017, 156:103-111
20. Fantes J, Ragge NK, Lynch SA, McGill NI, Collin JR, Howard-Peebles PN, Hayward C, Vivian AJ, Williamson K, van Heyningen V, FitzPatrick DR: [Mutations in *SOX2* cause anophthalmia.](https://www.ncbi.nlm.nih.gov/pubmed/12612584) Nat Genet. 2003, 33:461-463
21. Fraser FC, Schabtach G: 'Shrivelled', a hereditary degeneration of the lens in the house mouse. Genet Res. 1962, 3:383-387
22. Fukui HN, Obazawa H, Kinoshita JH: [Lens growth in the Nakano mouse.](https://www.ncbi.nlm.nih.gov/pubmed/1262174) Invest Ophthalmol. 1976, 15:422-425
23. Ganguly K, Favor J, Neuhäuser-Klaus A, Sandulache R, Puk O, Beckers J, Horsch M, Schädler S, Vogt Weisenhorn D, Wurst W, Graw J: [Novel allele of *Crybb2* in the mouse and its expression in the brain.](https://www.ncbi.nlm.nih.gov/pubmed/18385073) Invest Ophthalmol Vis Sci. 2008, 49:1533-1541
24. Gong X, Cheng C, Xia CH: [Connexins in lens development and cataractogenesis.](https://www.ncbi.nlm.nih.gov/pubmed/17578632) J Membr Biol. 2007, 218:9-12
25. Graw J, Bors W, Gopinath PM, Merkle S, Michel C, Reitmeir P, Schäffer E, Summer KH, Wulff A: Characterization of *Cat-2t*, a radiation-induced dominant cataract mutation in mice. Invest Ophthalmol Vis Sci. 1990a, 31:1353-1361.
26. Graw J, Werner T, Merkle S, Reitmeir P, Schäffer E, Wulff A: [Histological and biochemical characterization of the murine cataract mutant *Nop*.](https://www.ncbi.nlm.nih.gov/pubmed/2373148) Exp Eye Res. 1990b, 50:449-456
27. Graw J, Löster J, Soewarto D, Fuchs H, Meyer B, Reis A, Wolf E, Balling R, Hrabé de Angelis M: [Characterization of a new, dominant V124E mutation in the mouse aA-crystallin-encoding gene.](https://www.ncbi.nlm.nih.gov/pubmed/11687536) Invest Ophthalmol Vis Sci. 2001, 42:2909-2915
28. Graw J, Neuhäuser-Klaus A, Klopp N, Selby PB, Löster J, Favor J: [Genetic and allelic heterogeneity of Cryg mutations in eight distinct forms of dominant cataract in the mouse.](https://www.ncbi.nlm.nih.gov/pubmed/15037589) Invest Ophthalmol Vis Sci. 2004, 45:1202-1213
29. Halder C, Callaerts P, Gehring WJ: Induction of ectopic eyes by targeted expression of the eyeless gene in *Drosophila. Science* 1995, 267:1788-l 792.
30. Heermann T, Garrett L, Wurst W, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Graw J, Hölter SM: [*Crybb2* mutations consistently affect schizophrenia endophenotypes in mice.](https://www.ncbi.nlm.nih.gov/pubmed/30291584) Mol Neurobiol. 2018; doi: 10.1007/s12035-018-1365-5
31. Hertwig P: Neue Mutationen und kopplungsgruppen bei der Hausmaus. Z. induct. Abstammungs- u. Vererbungsl. 1942, 80:220-246
32. Hill RE, Favor J, Hogan BL, Ton CC, Saunders GF, Hanson IM, Prosser J, Jordan T, Hastie ND, van Heyningen V: [Mouse small eye results from mutations in a paired-like homeobox-containing gene.](https://www.ncbi.nlm.nih.gov/pubmed/1684639) Nature. 1991, 354:522-525; *erratum* in: [Nature. 1992, 355:750](https://www.ncbi.nlm.nih.gov/pubmed/1346927)
33. [Hodgkinson CA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hodgkinson%20CA%5BAuthor%5D&cauthor=true&cauthor_uid=8343963), [Moore KJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Moore%20KJ%5BAuthor%5D&cauthor=true&cauthor_uid=8343963), [Nakayama A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nakayama%20A%5BAuthor%5D&cauthor=true&cauthor_uid=8343963), [Steingrímsson E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Steingr%C3%ADmsson%20E%5BAuthor%5D&cauthor=true&cauthor_uid=8343963), [Copeland NG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Copeland%20NG%5BAuthor%5D&cauthor=true&cauthor_uid=8343963), [Jenkins NA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jenkins%20NA%5BAuthor%5D&cauthor=true&cauthor_uid=8343963), [Arnheiter H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Arnheiter%20H%5BAuthor%5D&cauthor=true&cauthor_uid=8343963): Mutations at the mouse microphthalmia locus are associated with defects in a gene encoding a novel basic-helix-loop-helix-zipper protein. [Cell.](https://www.ncbi.nlm.nih.gov/pubmed/?term=hodgkinson+ca+1993) 1993, 74:395-404
34. Hogan BL, Horsburgh G, Cohen J, Hetherington CM, Fisher G, Lyon MF: [Small eyes (*Sey*): a homozygous lethal mutation on chromosome 2 which affects the differentiation of both lens and nasal placodes in the mouse.](https://www.ncbi.nlm.nih.gov/pubmed/3794606) J Embryol Exp Morphol. 1986, 97:95-110
35. Hrabé de Angelis M, Balling R: [Large scale ENU screens in the mouse: genetics meets genomics.](https://www.ncbi.nlm.nih.gov/pubmed/9685575) Mutat Res. 1998, 400:25-32
36. [Jadeja S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jadeja%20S%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Smyth I](https://www.ncbi.nlm.nih.gov/pubmed/?term=Smyth%20I%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Pitera JE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pitera%20JE%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Taylor MS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taylor%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [van Haelst M](https://www.ncbi.nlm.nih.gov/pubmed/?term=van%20Haelst%20M%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Bentley E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bentley%20E%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [McGregor L](https://www.ncbi.nlm.nih.gov/pubmed/?term=McGregor%20L%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Hopkins J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hopkins%20J%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Chalepakis G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chalepakis%20G%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Philip N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Philip%20N%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Perez Aytes A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Perez%20Aytes%20A%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Watt FM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Watt%20FM%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Darling SM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Darling%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Jackson I](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jackson%20I%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Woolf AS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Woolf%20AS%5BAuthor%5D&cauthor=true&cauthor_uid=15838507), [Scambler PJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Scambler%20PJ%5BAuthor%5D&cauthor=true&cauthor_uid=15838507): Identification of a new gene mutated in Fraser syndrome and mouse myelencephalic blebs. [Nat Genet.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jadeja+s+2005) 2005, 37:520-525
37. Kador PF, Fukui HN, Fukushi S, Jernigan HM Jr, Kinoshita JH: [Philly mouse: a new model of hereditary cataract.](https://www.ncbi.nlm.nih.gov/pubmed/7363969) Exp Eye Res. 1980, 30:59-68
38. Knowlton MN, Smith CL: [Naming CRISPR alleles: endonuclease-mediated mutation nomenclature across species.](https://www.ncbi.nlm.nih.gov/pubmed/28589392) Mamm Genome. 2017, 28:367-376
39. Kratochvilova J: [Dominant cataract mutations detected in offspring of gamma-irradiated male mice.](https://www.ncbi.nlm.nih.gov/pubmed/7035547) J Hered. 1981, 72:302-307
40. [Kuck JF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kuck%20JF%5BAuthor%5D&cauthor=true&cauthor_uid=7346236), [Kuwabara T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kuwabara%20T%5BAuthor%5D&cauthor=true&cauthor_uid=7346236), [Kuck KD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kuck%20KD%5BAuthor%5D&cauthor=true&cauthor_uid=7346236): The Emory mouse cataract: an animal model for human senile cataract. [Curr Eye Res.](https://www.ncbi.nlm.nih.gov/pubmed/?term=kuck+1981+emory) 1981-1982, 1:643-649
41. Kunze S, Dalke C, Fuchs H, Klaften M, Rössler U, Hornhardt S, Gomolka M, Puk O, Sabrautzki S, Kulka U, Hrabě de Angelis M, Graw J: [New mutation in the mouse *Xpd*/*Ercc2* gene leads to recessive cataracts.](https://www.ncbi.nlm.nih.gov/pubmed/25951169) PLoS One. 2015, 10:e0125304
42. Little CC, Bagg HJ: The occurrence of two heritable types of abnormality among descendants of X-rayed mice. Am J Roentgenol. 1923, 10:975-989
43. [Llorente-González S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Llorente-Gonz%C3%A1lez%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22267908), [Peralta-Calvo J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peralta-Calvo%20J%5BAuthor%5D&cauthor=true&cauthor_uid=22267908), [Abelairas-Gómez JM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Abelairas-G%C3%B3mez%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=22267908): Congenital anophthalmia and microphthalmia: epidemiology and orbitofacial rehabilitation. [Clin Ophthalmol.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Llorente-Gonz%C3%A1lez+2011) 2011, 5:1759-1765
44. Lou MF: [Redox regulation in the lens.](https://www.ncbi.nlm.nih.gov/pubmed/12892645) Prog Retin Eye Res. 2003, 22:657-682
45. Lyon MF, Jarvis SE, Sayers I, Holmes RS: [Lens opacity: a new gene for congenital cataract on chromosome 10 of the mouse.](https://www.ncbi.nlm.nih.gov/pubmed/7333462) Genet Res. 1981, 38:337-341
46. Magabo KS, Horwitz J, Piatigorsky J, Kantorow M: [Expression of bB2-crystallin mRNA and protein in retina, brain, and testis.](https://www.ncbi.nlm.nih.gov/pubmed/10967064) Invest Ophthalmol Vis Sci. 2000, 41:3056-3060
47. Mathers PH, Grinberg A, Mahon KA, Jamrich M: [The *Rx* homeobox gene is essential for vertebrate eye development.](https://www.ncbi.nlm.nih.gov/pubmed/9177348) Nature. 1997, 387:603-607
48. Matteson PG, Desai J, Korstanje R, Lazar G, Borsuk TE, Rollins J, Kadambi S, Joseph J, Rahman T, Wink J, Benayed R, Paigen B, Millonig JH: [The orphan G protein-coupled receptor, *Gpr161*, encodes the *vacuolated lens* locus and controls neurulation and lens development.](https://www.ncbi.nlm.nih.gov/pubmed/18250320) Proc Natl Acad Sci USA. 2008, 105:2088-2093
49. McGregor L, Makela V, Darling SM, Vrontou S, Chalepakis G, Roberts C, Smart N, Rutland P, Prescott N, Hopkins J, Bentley E, Shaw A, Roberts E, Mueller R, Jadeja S, Philip N, Nelson J, Francannet C, Perez-Aytes A, Megarbane A, Kerr B, Wainwright B, Woolf AS, Winter RM, Scambler PJ: [Fraser syndrome and mouse blebbed phenotype caused by mutations in *FRAS1*/*Fras1* encoding a putative extracellular matrix protein.](https://www.ncbi.nlm.nih.gov/pubmed/12766769) Nat Genet. 2003, 34:203-208
50. [Mori M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mori%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23631845), [Gotoh S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gotoh%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23631845), [Taketani S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taketani%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23631845), [Hiai H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hiai%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23631845), [Higuchi K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Higuchi%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23631845): Hereditary cataract of the Nakano mouse: Involvement of a hypomorphic mutation in the coproporphyrinogen oxidase gene. [Exp Eye Res.](https://www.ncbi.nlm.nih.gov/pubmed/?term=mori+m+2013+cataract) 2013, 112:45-50
51. Nishimoto H, Uga S, Miyata M, Ishikawa S, Yamashita K: [Morphological study of the cataractous lens of the senescence accelerated mouse.](https://www.ncbi.nlm.nih.gov/pubmed/8299981) Graefes Arch Clin Exp Ophthalmol. 1993, 231:722-728
52. Oda S, Watanabe K, Fujisawa H, Kameyama Y: [Impaired development of lens fibers in genetic microphthalmia, eye lens obsolescence, *Elo*, of the mouse.](https://www.ncbi.nlm.nih.gov/pubmed/7215463) Exp Eye Res. 1980, 31:673-681
53. Phillips RJS: Blebbed, *bl*. Mouse News Lett. 1970, 42:26
54. Puk O, Dalke C, Favor J, de Angelis MH, Graw J: [Variations of eye size parameters among different strains of mice.](https://www.ncbi.nlm.nih.gov/pubmed/16897341) Mamm Genome. 2006, 17:851-857
55. Puk O, Ahmad N, Wagner S, Hrabé de Angelis M, Graw J: [First mutation in the βA2-crystallin encoding gene is associated with small lenses and age-related cataracts.](https://www.ncbi.nlm.nih.gov/pubmed/21212184) Invest Ophthalmol Vis Sci. 2011a, 52:2571-2576
56. Puk O, Ahmad N, Wagner S, de Angelis MH, Graw J: [Microphakia and congenital cataract formation in a novel Lim2(C51R) mutant mouse.](https://www.ncbi.nlm.nih.gov/pubmed/21617753) Mol Vis. 2011b, 17:1164-1171.
57. Ragge NK, Lorenz B, Schneider A, Bushby K, de Sanctis L, de Sanctis U, Salt A, Collin JR, Vivian AJ, Free SL, Thompson P, Williamson KA, Sisodiya SM, van Heyningen V, Fitzpatrick DR: SOX2 anophthalmia syndrome. Am J Med Genet A. 2005, 135:1-7
58. [Ramsing M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ramsing%20M%5BAuthor%5D&cauthor=true&cauthor_uid=2155726), [Rehder H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rehder%20H%5BAuthor%5D&cauthor=true&cauthor_uid=2155726), [Holzgreve W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Holzgreve%20W%5BAuthor%5D&cauthor=true&cauthor_uid=2155726), [Meinecke P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Meinecke%20P%5BAuthor%5D&cauthor=true&cauthor_uid=2155726), [Lenz W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lenz%20W%5BAuthor%5D&cauthor=true&cauthor_uid=2155726): Fraser syndrome (cryptophthalmos with syndactyly) in the fetus and newborn. [Clin Genet.](https://www.ncbi.nlm.nih.gov/pubmed/?term=ramsing+m+1990) 1990, 37:84-96
59. Rieger DK, Reichenberger E, McLean W, Sidow A, Olsen BR: [A double-deletion mutation in the Pitx3 gene causes arrested lens development in aphakia mice.](https://www.ncbi.nlm.nih.gov/pubmed/11247667) Genomics. 2001, 72:61-72
60. Roberts RC: *Small eyes* – a new dominant eye mutant in the mouse. Genet. Res., Camb. 1967, 9:121-122
61. Rosemann M, Ivashkevich A, Favor J, Dalke C, Hölter SM, Becker L, Rácz I, Bolle I, Klempt M, Rathkolb B, Kalaydjiev S, Adler T, Aguilar A, Hans W, Horsch M, Rozman J, Calzada-Wack J, Kunder S, Naton B, Gailus-Durner V, Fuchs H, Schulz H, Beckers J, Busch DH, Burbach JP, Smidt MP, Quintanilla-Martinez L, Esposito I, Klopstock T, Klingenspor M, Ollert M, Wolf E, Wurst W, Zimmer A, de Angelis MH, Atkinson M, Heinzmann U, Graw J: [Microphthalmia, parkinsonism, and enhanced nociception in *Pitx3416insG* mice.](https://www.ncbi.nlm.nih.gov/pubmed/20033184) Mamm Genome. 2010, 21:13-27
62. Semina EV, Murray JC, Reiter R, Hrstka RF, Graw J: [Deletion in the promoter region and altered expression of Pitx3 homeobox gene in aphakia mice.](https://www.ncbi.nlm.nih.gov/pubmed/10861284) Hum Mol Genet. 2000, 9:1575-1585
63. Sheeladevi S, Lawrenson JG, Fielder AR, Suttle CM: [Global prevalence of childhood cataract: a systematic review.](https://www.ncbi.nlm.nih.gov/pubmed/27518543) Eye (Lond). 2016, 30:1160-1169
64. Smyth I, Du X, Taylor MS, Justice MJ, Beutler B, Jackson IJ: [The extracellular matrix gene Frem1 is essential for the normal adhesion of the embryonic epidermis.](https://www.ncbi.nlm.nih.gov/pubmed/15345741) Proc Natl Acad Sci USA. 2004, 101:13560-13565
65. Solebo AL, Teoh L, Rahi J: [Epidemiology of blindness in children.](https://www.ncbi.nlm.nih.gov/pubmed/28465303) Arch Dis Child. 2017, 102:853-857
66. Steingrímsson E, Copeland NG, Jenkins NA: [Melanocytes and the microphthalmia transcription factor network.](https://www.ncbi.nlm.nih.gov/pubmed/15568981) Annu Rev Genet. 2004, 38:365-411
67. [Sun M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sun%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Hölter SM](https://www.ncbi.nlm.nih.gov/pubmed/?term=H%C3%B6lter%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Stepan J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Stepan%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Garrett L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Garrett%20L%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Genius J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Genius%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Kremmer E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kremmer%20E%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Hrabě de Angelis M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hrab%C4%9B%20de%20Angelis%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Wurst W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wurst%20W%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Lie DC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lie%20DC%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Bally-Cuif L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bally-Cuif%20L%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Eder M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Eder%20M%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Rujescu D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rujescu%20D%5BAuthor%5D&cauthor=true&cauthor_uid=24096375), [Graw J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Graw%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24096375): *Crybb2* coding for βB2-crystallin affects sensorimotor gating and hippocampal function. [Mamm Genome.](https://www.ncbi.nlm.nih.gov/pubmed/?term=sun+m+2013+graw) 2013, 24:333-348
68. [Sun M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sun%20M%5BAuthor%5D&cauthor=true&cauthor_uid=29864422), [Ahmad N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ahmad%20N%5BAuthor%5D&cauthor=true&cauthor_uid=29864422), [Zhang R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20R%5BAuthor%5D&cauthor=true&cauthor_uid=29864422), [Graw J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Graw%20J%5BAuthor%5D&cauthor=true&cauthor_uid=29864422): *Crybb2* associates with *Tmsb4X* and is crucial for dendrite morphogenesis. [Biochem Biophys Res Commun.](https://www.ncbi.nlm.nih.gov/pubmed/?term=sun+m+2018+graw) 2018, 503:123-130
69. Takamiya K, Kostourou V, Adams S, Jadeja S, Chalepakis G, Scambler PJ, Huganir RL, Adams RH: [A direct functional link between the multi-PDZ domain protein GRIP1 and the Fraser syndrome protein Fras1.](https://www.ncbi.nlm.nih.gov/pubmed/14730302) Nat Genet. 2004, 36:172-177
70. Takeda T, Hosokawa M, Takeshita S, Irino M, Higuchi K, Matsushita T, Tomita Y, Yasuhira K, Hamamoto H, Shimizu K, Ishii M, Yamamuro T: [A new murine model of accelerated senescence.](https://www.ncbi.nlm.nih.gov/pubmed/7311623) Mech Ageing Dev. 1981, 17:183-194
71. [Taranova OV](https://www.ncbi.nlm.nih.gov/pubmed/?term=Taranova%20OV%5BAuthor%5D&cauthor=true&cauthor_uid=16651659), [Magness ST](https://www.ncbi.nlm.nih.gov/pubmed/?term=Magness%20ST%5BAuthor%5D&cauthor=true&cauthor_uid=16651659), [Fagan BM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fagan%20BM%5BAuthor%5D&cauthor=true&cauthor_uid=16651659), [Wu Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wu%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=16651659), [Surzenko N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Surzenko%20N%5BAuthor%5D&cauthor=true&cauthor_uid=16651659), [Hutton SR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hutton%20SR%5BAuthor%5D&cauthor=true&cauthor_uid=16651659), [Pevny LH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pevny%20LH%5BAuthor%5D&cauthor=true&cauthor_uid=16651659). SOX2 is a dose-dependent regulator of retinal neural progenitor competence. [Genes Dev.](https://www.ncbi.nlm.nih.gov/pubmed/?term=taranova+ov+2006) 2006, 20:1187-1202
72. Tucker P, Laemle L, Munson A, Kanekar S, Oliver ER, Brown N, Schlecht H, Vetter M, Glaser T: [The *eyeless* mouse mutation (*ey1*) removes an alternative start codon from the Rx/rax homeobox gene.](https://www.ncbi.nlm.nih.gov/pubmed/11668677) Genesis. 2001, 31:43-53
73. Varnum DS, Stevens LC: Aphakia, a new mutation in the mouse. J Hered. 1968, 59:147-150
74. [Winter RM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Winter%20RM%5BAuthor%5D&cauthor=true&cauthor_uid=2166630): Fraser syndrome and mouse 'bleb' mutants. [Clin Genet.](https://www.ncbi.nlm.nih.gov/pubmed/2166630) 1990, 37:494-495
75. Yan X, Sabrautzki S, Horsch M, Fuchs H, Gailus-Durner V, Beckers J, Hrabě de Angelis M, Graw J: [Peroxidasin is essential for eye development in the mouse.](https://www.ncbi.nlm.nih.gov/pubmed/24895407) Hum Mol Genet. 2014;23:5597-5614

**Table 1:**

**Unsolved mutants for anophthalmia/microphthalmia and microphthalmia/cataract\***

|  |  |  |  |
| --- | --- | --- | --- |
| Gene symbol | Anophthalmia/  microphthalmia | Micropthalmia/  cataract | Strain available (if and where) |
| *Alm* |  | anterior lenticonus with microphthalmia | extinct |
| *B2b1511* | anopthalmia, microphthalmia |  | JAX |
| *B2b1702* | anopthalmia, microphthalmia |  | extinct |
| *B2b1963* | anopthalmia, microphthalmia |  | JAX |
| *B2b2012* | cyclops, anopthalmia, microphthalmia |  | extinct |
| *B2b2110* | anopthalmia, microphthalmia |  | JAX |
| *B2b2153* | enophthalmia, anopthalmia, microphthalmia |  | JAX |
| *B2b2739* | anopthalmia, microphthalmia |  | JAX |
| *bh* | brain hernia | brain hernia | extinct |
| *Bld* |  | blind | extinct |
| *Cat3* |  | cataract 3 | HMGU |
| *dblr* | doubleridge |  | extinct |
| *dcm* |  | dense cataract and microphthalmia | extinct |
| *eob* |  | eye lids open at birth | extinct |
| *exma* | exencephaly with severe micropthalmia/anopthalmia |  | extinct |
| *ey2* | eyeless 2 |  | extinct |
| *Ey3* | eyeless 3 |  | JAX |
| *ey4* | eyeless 4 |  | JAX |
| *eyl2* | eyeless 2 Jackson |  | JAX |
| *Iac* |  | iris anomaly with cataract | extinct |
| *Idc* |  | iris dysplasia with cataract | extinct |
| *jrc* |  | juvenile recessive cataract | extinct |
| *Lcl* |  | lens cloudy | Harwell, EMMA |
| *lg* | lid gap | lid gap | extinct |
| *nmf131* |  | cataract, microphthalmia | JAX |
| *Pcs* |  | Polar cataract and small eyes | extinct |
| *Rgsc258* |  | cataract, microphthalmia | RIKEN |
| *Rgsc152* |  | cataract, microphthalmia | RIKEN |
| *Rgsc1371* |  | cataract, microphthalmia | RIKEN |
| *Rgsc1465* |  | cataract, microphthalmia | RIKEN |
| *Tcm* |  | Total cataract with microphthalmia | extinct |
| *tirs* | tiresias |  | extinct |

\*Data are from the Mammalian Phenotype Ontology Associations of the Mouse Genome Informatics database (http://www.informatics.jax.org/vocab/mp\_ontology) using the search terms “anophthalmia”, “microphthalmia” and “cataract” (Sept. 25, 2018).

**Resources for mouse mutants:**

**EMMA:** The European Mouse Mutant Archive; c/o Helmholtz Center Munich, Institute of Experimental Genetics; Neuherberg/Germany; https://www.infrafrontier.eu/search

**Harwell:** MRC Harwell; Harwell Science and Innovation Campus, Harwell/UK; http://www.mousebook.org/stock-list

**HMGU:** Helmholtz Center Munich, Institute of Developmental Genetics; Neuherberg/Germany; <http://www.helmholtz-muenchen.de/en/idg/research/neuropsychiatric-diseases/eye-disease/research/index.html>

**JAX:** The Jackson Laboratory, Bar Harbor, USA; https://www.jax.org/orderform

**RIKEN:** Riken BioResource Research Center, Tsukuba/Japan; http://mus.brc.riken.jp/en/order

**Legend to the figures**

Fig. 1: **Anophthalmia mouse mutant.**

Head of a neonatal homozygous *Pax6Aey11* mutant compared to a wild-type mouse (wt) at the same age. The absence of eyes in the mutant is obvious. The eyelids of neonatal mice are still closed (photography: Jana Löster†, unpublished).

Fig. 2: **Morphology of the *eyeless* mouse – a model for microphthalmia.**

a) The mutant mice have closed eyelids with very small eyes (microphthalmia). b-e) Heterozygous and homozygous *eyeless* mutants are compared at embryonic day 14.5. In the upper panel, it is obvious that the eye of the homozygous mutant (c) is much smaller than the wild-type eye (b). In the lower panel, a transverse section through the eye is given (H/E staining): in contrast to the regularly formed wild-type eye (d), the eye of the homozygous mutants (e) is highly disorganized: the cornea is thicker, the lens is largely missing (only a remnant is present), and the retina is hypertrophic filling most of the vitreous body.

C, cornea; L, lens; R: retina. (from Rosemann et al., 2010, with permission from Springer Science+Business Media, LLC 2009)

Fig. 3: **Cataracts in *Ercc2Rco015* mutant mice**

a) Lenses of 5-week old wild types, hetero- and homozygous *RCO015* mutants are prepared and photographed. The lenses of wild types are completely clear; the lenses of heterozygous mutants demonstrate opacities at the capsule, and in the homozygous mutants clear boundaries in the cortical areas are observed in addition to the nuclear opacity. The lenses of homozygous mutants are smaller (bar: 500 µm).

b) Scheimpflug imaging of the same lenses as shown in a) demonstrates the clear lenses in wild types and heterozygotes; the opacity in the nuclear region of homozygous mutants is clearly visible above the slightly opaque background of the entire lens.

c) The quantitative data of the lens density of the Scheimpflug images are given in a box-and-whisker plot; the whiskers give the 1st and 3rd quartiles, and the bar in the middle of the box indicates the median of the lens density. (from Kunze et al., 2015, with permission from the authors).

**Figures**

Fig. 1:

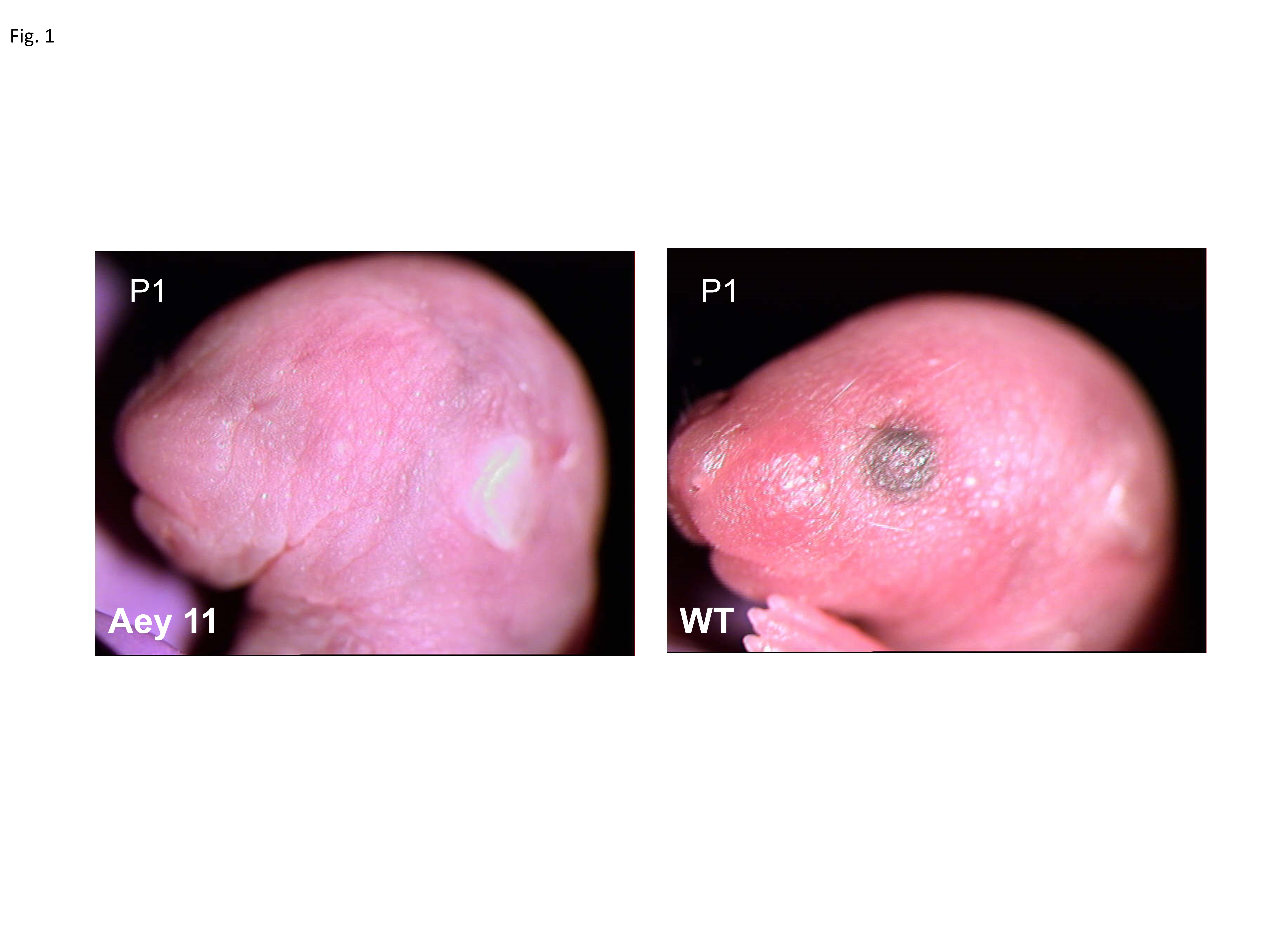


Fig. 2:

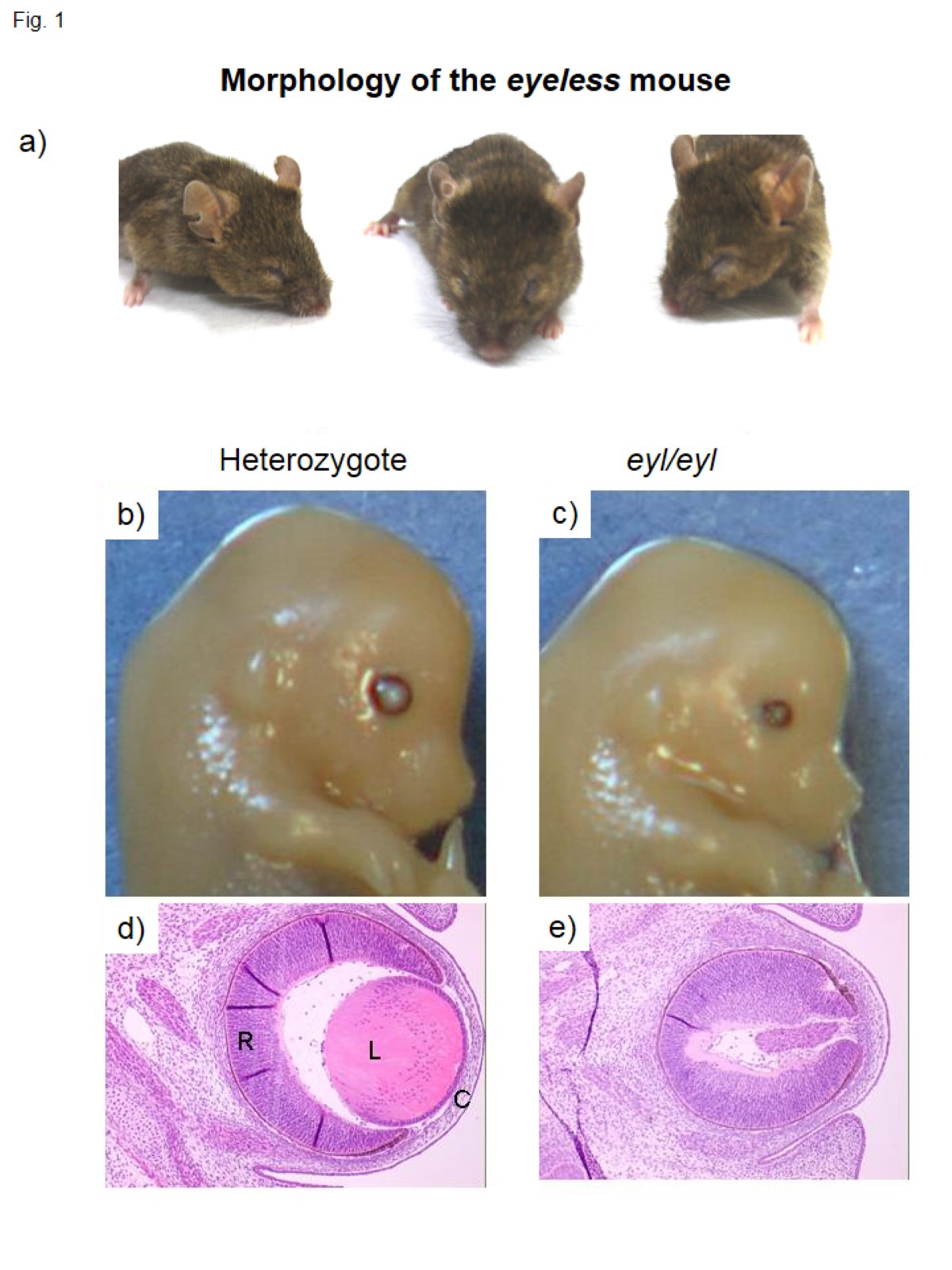


Fig. 3:

