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Congenital hereditary cataracts

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ABSTRACT Congenital cataracts are rare and occur in developed countries with a frequency of 30 cases among 100,000 births with a further 10 cases being diagnosed during childhood. They reflect mainly genetically caused developmental alterations in the lens and surrounding ocular tissues. Even if modern Human Genetics has made large steps forward in the characterization of human hereditary disorders, the underlying developmental processes can only be investigated in model organisms. The mouse is such a good model because of its similarity (as a mammal) and its genetic characterization. This review brings together our genetic and developmental knowledge of congenital, human cataracts with the corresponding mouse models. First, early events will be influenced by genes coding for transcription factors like Pax6, Pitx3, Maf or Sox. If the lens is maturing, mutations affecting the lens membranes (aquaporins/Mip, Lim-2 or connexins) or the structural proteins of the cytosol of the lens fiber cells (the crystallins) become more important. From a genetic point of view it becomes obvious that cataract-causing mutations are not distributed randomly. The discovery of a broad variety of genes important for eye and lens development made much progress in the recent years. Nevertheless, there still remains a long list of mutations to be characterized and functionally investigated both in mouse and man indicating a broad genetic heterogeneity in that which clinicians simply refer to as a "cataract".

KEY WORDS: *lens, development, cataract, genetics*

Introduction

Cataracts as lens opacities are a group of well-known diseases since centuries; particularly in the elderly population the frequency is quite common. There are a lot of ongoing epidemiological studies to figure out risk factors; however, there are only a few factors recognized like UV-B exposure, low antioxidant intake, certain medications, cigarette smoking, diabetes and gout as well as family history (McCarty, 2003).

In contrast to these age-related forms of cataract, congenital cataracts or cataracts in early childhood are rather rare and occur in developed countries with a frequency of 30 cases among 100.000 births; with a further 10 cases being diagnosed by the age of 15 years (mainly as dominant forms). Rates are likely to be higher in developing countries because of rubella infections and consanguinity (for the recessive forms; Foster *et al.*, 1997).

To learn more about developmental processes and their disease-causing disturbances, it is helpful to look for appropriate animal models. Such a model is the mouse: a mammal like human, but much smaller, with a shorter generation time and extremely well characterized from a genetic point of view. The first evaluation of large mouse populations for mutations affecting the eye lens at birth was initiated in 1979, when Kratochvilova and Ehling described for the first time the systematic screening for murine dominant cataract mutants in the F_1 generation after paternal radiation treatment. The systematic screening for eye mutants was extended to the use of ethylnitrosourea (ENU) as mutagenic agent (Ehling *et al.,* 1985; West and Fisher 1986). Some of the mutants were grouped into allelic series (Kratochvilova and Favor, 1992; Everett *et al.,* 1994; Favor 1995). All the mutant phenotypes characterized up to now are caused by single dominant gene mutations. Together with further mutants described in the literature, a mosaic can be built up reflecting important steps during lens development and differentiation. In this review mouse mutants suffering from hereditary, congenital (or early childhood cataract) will be discussed and compared to corresponding human disorders; however, transgenic models leading to cataract will not be included, because they are in the focus of the article by Paul Overbeek (this issue). An overview of mouse eye development is given in Fig. 1.

Abbreviations used in this paper: MARE, Maf responsive element.

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Mutations at early stages of lens development

Pax6 and Pitx3

One of the central genes in eye development is the paired-box gene *Pax6*, which was recognized as being affected in the mouse and rat *Small eye* (*Sey*) mutants (Hill *et al.,* 1991; Matsuo *et al.,* 1993). *Pax6* maps at mouse chromosome 2; the actual list of the Jackson Laboratory (http://www.informatics.jax.org/searches; April 2004) contains 25 alleles in the mouse, 4 of them are targeted mutations. In the "classical" *Sey* mutant, the failure in lens development is attributed to a defect in the inductive interaction between the optic vesicle and the overlying ectoderm, since these tissues fail to make discrete contacts (Hogan *et al.,* 1986). During embryogenesis, the heterozygotes express obvious microphthalmia with a triangular-shaped pupil, and homozygotes express anophthalmia with severe craniofacial defects (Hogan *et al.*, 1988). Homozygotes die around birth because of breathing problems.

Usually, the expressivity of heterozygous *Pax6*-mutations is variable with mutant carriers expressing a range of phenotypes from small anterior polar cataracts to the more extreme phenotype of anterior polar opacity, corneal adhesions, iris abnormalities and microphthalmia. Furthermore, the degree of phenotype expressed between the eyes of an individual mutation carrier was variable (Favor *et al.*, 2001).

In humans, *PAX6* mutations lead mainly to aniridia, cataracts and Peter's anomaly (Glaser *et al.*, 1994; Hanson and van Heyningen, 1995; Prosser and van Heyningen, 1998; Hanson *et al.*, 1999; van Heyningen and Williamson, 2002; Morrison *et al.*, 2002). Although further studies are needed to establish clear genotype-phenotype correlations, most mutations found to date affects exons 5 and 6 and their connecting intron region; a few mutations have also been found in the homeodomain. Genotype and phenotype information for human *PAX6* mutations is collected in a database, which contains more than 300 records (http://pax6.hgu.mrc.ac.uk/).

The morphological alterations correspond to the expression pattern of *Pax6*. *Pax6* transcripts are first detected in the presumptive fore- and hindbrain of 8-day-old mouse embryos; at E8.5 it is present in the optic sulcus, the lateral evagination at the basis of the forebrain. Later, at E9.5, *Pax6* is expressed in the optic vesicle, the optic stalk, and the surface ectoderm, which will give rise to the lens. Between E10 and E12, *Pax6* is observed in the inner layer of the optic cup, in the lens and in the surface ectoderm, which gives at this stage rise to the future cornea. In the elongating primary fiber cells, *Pax6* has a posterior localization. At E15.5, Pax6 is expressed in the two layers of the neural retina, the anterior epithelium of the cornea, and in the lens. Beside the eye, Pax6 occurs in specific regions of the brain, the olfactory epithelium, and the pancreas (Walther and Gruss, 1991; Hanson and van Heyningen, 1995; St.Onge *et al.*, 1997).

The second interesting gene in the context of early lens development is *Pitx3*. In the mouse mutant *aphakia* (*ak*; Varnum and Stevens, 1968), the promotor of the *Pitx3* gene is affected by two deletions (Semina *et al.*, 2000; Rieger *et al.*, 2001). The phenotype is characterized at early stages of development by a small lens vesicle with a stable contact to the cornea ("lens stalk"). In later stages, the lens vesicle is degraded which leads to the formation of a lens-less eye giving this mutant its name. Another mutant line, *Cat4*^{a}, shares one aspect with the *aphakia* mutant, the inhibition of the separation of the lens vesicle from the surface ectoderm (Grimes *et al.*, 1998). However, *Cat4*^{a} is mapped on mouse chromosome 8 (Favor *et al.*, 1997) suggesting to be different from *Pitx3*.

In contrast to the mouse situation, mutations in the human *PITX3* gene are causative for congenital cataracts; in one of the two cases reported the phenotype includes also anterior segment mesenchymal dysgenesis (Semina *et al.*, 1998). The phenotype of the mouse mutant as well as the disorders of the patients correlate to the expression pattern of the affected gene *Pitx3*. It is strongly expressed in the developing lens vesicle starting at day 11 of embryonic mouse development, but later also throughout the lens,

TABLE 1

MUTANT ALLELES CODING FOR MEMBRANE PROTEINS INVOLVED IN CONGENITAL CATARACTS

Name	*Allele Symbol*	Phenotype	Molecular lesion	Consequence for Protein	Reference
Mip	*Cat*^{Fr}	Progressive degeneration of lens fiber cells	E.Tn insertion→splicing defect	Fusion protein	Shiels & Bassnett, 1996
	Cat^{Lop}	Progressive degeneration of lens fiber cells	G151C Ala51Pro	Transmembrane domain 2	Shiels & Bassnett, 1996
	Hfi	Hydropic lens fibers (+/-) Total lens opacity (-/-)	76 bp deletion in intron 2 splicing defect	Loss of exon 2 Loss of transmembrane domains 4 & 5	Sidjanin *et al.*, 2001
	Cat^{Tohm}	Small eyes with opaque lenses	Δ137-148 ΔLAFG46-49	Transmembrane domain 2	Okamura *et al.*, 2003
MIP		Polymorphic lamellar cataract	C→G Thr138Arg	Transmembrane domain 4	Berry *et al.*, 2000
MIP		Polymorphic lamellar cataract	A→G Glu134Gly	Transmembrane domain 4	Berry *et al.*, 2000
Lim2	*To3*	Total opacity with a dense cataract	G44T Gly15Val	Transmembrane domain 1	Steele *et al.*, 1997
Gja1	*Gja1*$^{-/-}$*	Intracellular vacuoles	Targeted deletion	Loss of function	Gao and Spray 1998
	GJA1	Oculodentodigital syndrome	A50C Tyr17Ser	Cytoplasmatic N-terminus	Paznekas *et al.*, 2003#
Gja3	*Gja3*$^{-/-}$	Nuclear cataract	Targeted deletion	Loss of function	Gong *et al.*, 1997
GJA3		Zonular pulverulent cataract	C560T Pro187Leu	Transmembrane domain 2	Rees *et al.*, 2000
GJA3		Zonular pulverulent cataract	A188G Asn63Ser	1st extracellular loop	Mackay *et al.*, 1999
GJA3		Zonular pulverulent cataract	1137insC frameshift	Hybrid protein from codon 380	Mackay *et al.*, 1999
Gja8	*No2*	Nuclear and zonular cataract	A→C Asp→Ala	1st extracellular loop	Steele *et al.*, 1998
	Aey5	Nuclear and zonular cataract	T191C Val64Ala	1st extracellular loop	Graw *et al.*, 2001b
	Gja$^{-/-}$	microphthalmia and nuclear cataract	Targeted deletion	Loss of function	White *et al.*, 1998
GJA8		Zonular pulverulent cataract	C262T Pro88Ser	Transmembrane domain 2	Shiels *et al.*, 1998
GJA8		Zonular nuclear pulverulent cataract	G→A Glu48Lys	1st extracellular loop	Berry 1999

MP19, membrane protein of 19 KDa; Cx, Connexin; * There are some further conditional knockouts, but without relation to the eye; # In this reference, 16 further alleles are reported covering the entire *GJA1* gene and resulting in the same phenotype.

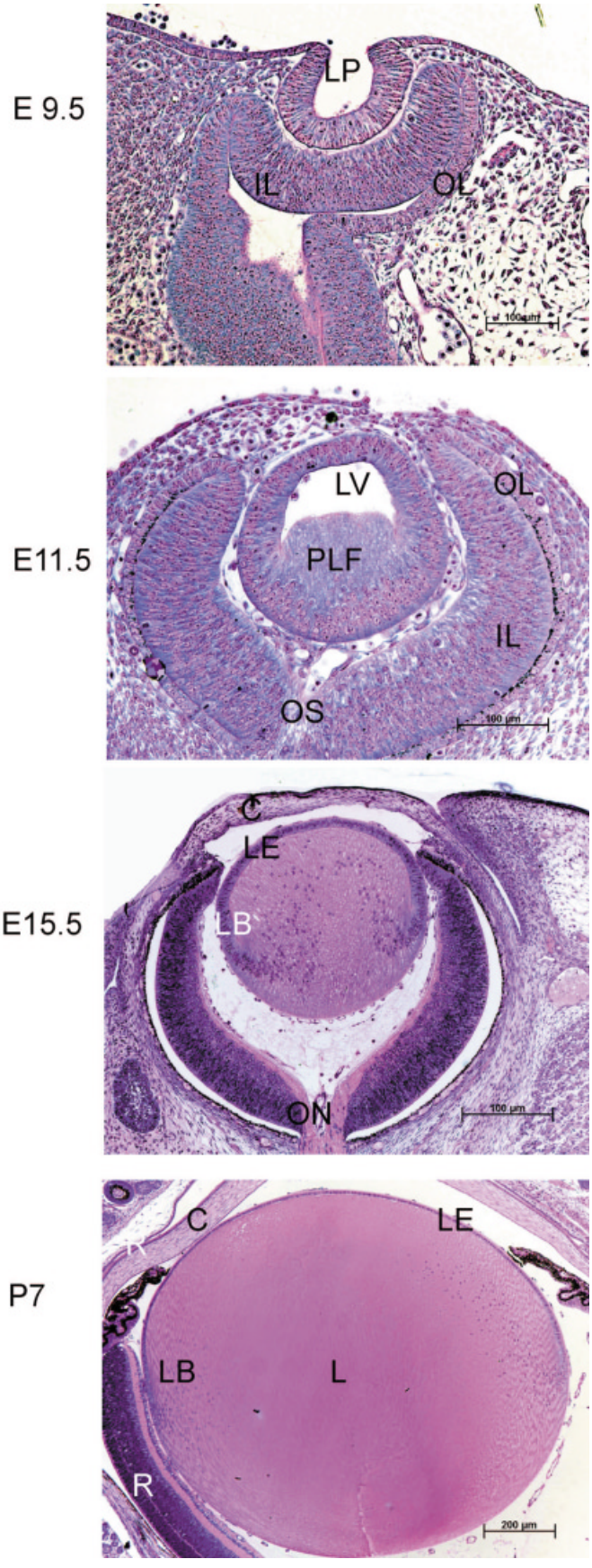

Fig. 1. Histological sections through a developing mouse eye. *At* **E 9.5**, *the lens placode invaginates forming the lens pit (LP); the underlying neuroectoderm follows this inward movement forming the inner layer (IL) of the optic cup. It will further develop into the neural part of the retina; the outer layer (OL) gives rise to the future pigment layer (or pigment epithelium) of the retina. When the lens vesicle (LV) is formed and detached from the surface ectoderm, the primary lens fibres (PLF) begin to elongate from the posterior part* **(E11.5)**. *The two layers (OL, IL) of the retina are closely attached, and the optic stalk (OS) maintains the connection to the diencephalon. When the lens vesicle is filled by the primary lens fibres, the epithelial cells divide and move to the lens equator. At the lens bow (LB) region, they elongate as they differentiate into secondary lens fibre cells. This process continues throughout life and leads to superficial layers of secondary fibre cells. The cell nuclei at* **E15.5** *are arranged in a wave-like manner through the lens. At that time, the cornea (C) is also present. The nerve fibres (NFL, nerve fibre layer of the optic cup) join to the optic nerve (ON), which is growing retrograde to the brain through the optic stalk. One week after birth* **(P7)**, *the eye is finally developed and the centre of the lens is free of cellular organells like nuclei or mitochondria (C, cornea; L, lens, LE, lens epithelium; LB, lens bow; R, retina). (Previously published by Graw and Löster, 2003).*

particularly in the anterior epithelium and equator region (Semina *et al.*, 1997). Moreover, there are recent reports that *Pitx3* is also expressed in the dopaminergic neurons of the *substatia nigra* in the brain (Nunes *et al.*, 2003); therefore, it is not surprising that *aphakia* mice suffer also from a selective loss of these particular neurons (Hwang *et al.*, 2003) and a malformation of the mesencephalic dopamine system (Smidt *et al.*, 2004).

Maf, Sox, Fox and Eya

There are some other genes coding for transcription factors important for eye and lens development, *Maf*, *Sox1*, *Sox2*, *FoxC1* and *FoxE3*. Particularly, Maf and Sox1 act as transcription factors on the promoters of the γ-crystallin encoding genes (*Cryg*).

The Fox-transcription factors are characterized by an 110-amino-acid motif originally defined as a DNA-binding domain in the *Drosophila* transcription factor forkhead (Fox: forkhead box). Recently, Blixt *et al.,* (2000) characterized a mutation in *FoxE3* to be causative for the phenotype in an old mouse mutant, *dysgenic lens* (*dyl*). In this mutant, the lens vesicle fails to separate from the ectoderm causing the lens and the cornea to fuse. In human, mutations in *FOXE3* lead to anterior segment ocular dysgenesis (Semina *et al.*, 2001). Similarly, mutations in the human *FOXC1* and corresponding mouse mutant lead to a similar phenotype with additional glaucoma (Nishimura *et al.*, 2001; Hong *et al.*, 1999).

The Maf family of basic region leucine zipper (bZIP) transcription factors was first identified through the *v-maf* oncogene, an avian retrovirus transforming gene (Nishizawa, *et al.*, 1989). In chicken and Xenopus, it was demonstrated by several authors that L-*MAF* is involved in the regulation of crystallin expression. L-Maf is first expressed at the lens placode and is maintained specifically in lens cells (Shimada *et al.*, 2003). The mouse homologue to the Xenopus L-*Maf* is obviously *Nrl* coding for a neural retina-specific leucine zipper protein; whereas the mouse homologue to the chicken L-*Maf* is *Maf*-B (NCBI UniGene). The third mammalian member of the Maf family demonstrating important properties concerning lens development is c-*Maf*. The targeted deletion of c-Maf in the mouse leads to a stop of lens primery fiber cell elongation at the lens vesicle stage (Ring *et al.*, 2000); the same feature was

published recently for a mild pulverulent cataract mutant in mouse (opaque flecks in the lens, *Opj;* Lyon *et al.*, 2003). The point mutation affects the basic region of the DNA-binding domain.

In general, Maf binds as homo- or heterodimer to two known Maf responsive elements (MAREs), with varying affinities and transactivation potentials (Kataoka *et al.*, 1993; 1996). MAREs are found in the promoters of the crystallin-encoding genes and *Pitx3* (Semina *et al.*, 2000; Ogino *et al.*, 1998). Recently, two families were identified suffering from ocular developmental abnormalities (in one case, cataract is associated with anterior segment dysgenesis and microphthalmia; in the other case, cataract is associated with microcornea and iris coloboma). In the first family, congenital cataract co-segregated with a translocation; its breakpoint on 16q23 lies close to the lens-development gene, *MAF*, and transects the common fragile site *FRA16D* (Jamieson *et al.*, 2002). In the second family, a causative mutation for congenital cataract (observed over three generations) was identified affecting the DNA-binding domain of MAF (Jamieson *et al.*, 2002). These findings implicate *MAF* as a disease gene in the complex pathway of transcriptional regulatory genes involved in lens and anterior segment development.

The Sox-family of transcription factors has a HMG domain (high mobility group) in common; the founder of this family is the *Sry* gene (sex-determining region of Y chromosome; Koopman, 1999). The genes *Sox1*, *Sox2* and *Sox3* belong to subgroup B (Kamachi *et al.*, 2000); they are expressed in the mouse in the central nervous system and in the sensory placodes. Particularly, *Sox2* is expressed during early eye development in the lens placode in the portion of the ectoderm that is in contact with the optic cup and invaginates to form the lens vesicle. This invagination coincides with the onset of *Sox1* expression in the mouse lens placode. At later stages, *Sox2* is downregulated and Sox1 comes up (Kamachi *et al.*, 1998).

A targeted deletion of *Sox1* in mice caused microphthalmia and cataract. Mutant lens fiber cells fail to elongate, probably as a result of an almost complete absence of *Cryg* transcripts (Nishiguchi *et al.,* 1998). The phenotype of the homozygous *Sox1* deletion mutant is very similar to the most severe *Cryg* mutation, *Cryge*^{t}. In contrast to *Sox1*, mutations in the human *SOX2* gene cause anophthalmia (without cataract; Fantes *et al.*, 2003), however, the heterozygous knockout mice of *Sox2* appeared normal, but the homozygous mutants are peri-implantationally lethal (Avilion *et al.*, 2003).

Another mammalian family of genes has close relationship to a *Drosophila* gene: eyes absent. In mouse and man four members belong to this family *(Eya1-4*), but so far only a mutation in the human *EYA1* gene is reported to lead to cataract (together with Peter's anomaly and nystagmus; Azuma *et al.*, 2000).

Miscellaneous

In addition, there are several other genes (e. g. *Shh*, *rx/eyeless*, *Lhx, Bmp4* or *Bmp7*) known to be expressed at these early stages; however, the phenotypes of the corresponding knock-out or null-mutants are causing mainly anophthalmia (the loss of the entire ocular structure) or microphthalmia (small eye), but no cataracts. For further discussion of these genes refer to previous reviews and references therein (e.g. Graw, 2003).

After the lens placode stage, the next important step is the formation of the lens vesicle. Its key role is addressed by some mouse mutants like *extra toes* (*Gli3*^{Xt}*;* Franz and Besecke, 1991), *eye lens aplasia* (*elap*; Aso *et al.,* 1995, 1998), *head blebs* (*heb;* Varnum and Fox, 1981) or *myelencephalic blebs* (*my;* Center and Polizotto, 1992). All these mouse models have in common a microphthalmic phenotype with major disturbances on most of the ocular tissues. The lens is frequently missing; correspondingly, these mutations are not associated with cataracts. One of them is molecularly characterized (*extra toes*; *Gli3*; Hui and Joyner, 1993).

Mutations affecting lens membranes

As demonstrated above, only in a few cases cataracts are formed at the early stages of eye development. However, one might assume that more and diverse phenotypes of cataracts occur, if stages are affected, when the lens vesicle is already formed. In this chapter those mutants are described affecting the membrane of lens cells (an overview is given in Tab. 1).

Aquaporin/MIP

One of the first detected cataract mutations is the *Cataract Fraser* (*Cat*^{Fr}; Fraser and Schabtach, 1962). In this mutant, the cell nuclei in the deep cortex become abnormally pycnotic (beginning at E14), degeneration of cytoplasm and destruction of the lenticular nucleus follow (Zwaan and Williams, 1969). *Cat*^{Fr} was shown to be allelic with another mouse mutant, referred to as *Lens opacity* (*Lop*). The two alleles, *Cat*^{Lop} and *Cat*^{Fr}, were mapped 20 cM distal to *Steel* (*Sl*) at chromosome 10 (Lyon *et al.,* 1981; Muggleton-Harris *et al.,* 1987). A candidate gene for the *Cat* locus encodes the membrane intrinsic protein (gene symbol: *Mip*; Griffin and Shiels, 1992). Sequence analysis revealed that the *Cat*^{Fr} mutation is due to a transposon-induced splicing error leading to a truncated form of *Mip* transcripts. However, the mutation in the *Cat*^{Lop} leads to a single amino-acid substitution, which inhibits targeting of Mip to the cell membrane (Shiels and Griffin, 1993; Shiels and Bassnett, 1996). Recently, a new mutant allele (*Cat*^{Tohm}) was reported, which is characterized by a 12 bp deletion and a corresponding loss of 4 amino acids within the second transmembrane region (Okamura *et al.*, 2003). Mip forms specialized junctions between the fiber cells and can be first detected in the primary fiber cells of the early lens vesicle. In *situ hybridization* demonstrated that *Mip* expression is highest in the elongating fiber cells in the bow region of the lens; Mip antiserum specifically decorates fiber cell membranes, highlighting their regular anterior to posterior organization (Shiels and Griffin, 1993; Zhou *et al.*, 2002). Mip is also referred to aquaporin; a recent review was published by Agre and Kozono (2003)

LIM

The *total opacity To3* is placed on chromosome 7 (Kerscher *et al.,* 1996). Mice heterozygous or homozygous for the *To3* mutation exhibit a total opacity of the lens with a dense cataract. Additionally, homozygotes exhibit microphthalmia and abnormally small eyes. Histological analysis revealed vacuolization of the lens and gross disorganization of the fibers; posterior lens rupture can be observed only in homozygotes. The *To3* mutation was characterized as a single G→T transversion within the first exon of the *Lim2* gene coding for a lens-specific integral membrane protein, MP19. It was predicted that this DNA change results in a nonconservative substitution of a valin for the normally encoded glycine at amino acid #15 of the MP19 protein (Steele *et al.,* 1997). *Lim2* mRNA can

be found in the head region of mouse embryos from embryonic day 12 on (Zhou *et al.*, 2002). In human, a missense mutation in the *LIM2* gene is associated with autosomal recessive presenile cataract (Pras *et al.*, 2002).

Connexins in the lens

The *Gja8* gene encodes the lens-specific gap junction membrane channel protein α8, which is also referred to as connexin 50 or MP70. It maps to mouse chromosome 3 (Kerscher *et al.,* 1995) and was demonstrated recently to be affected by a single A→C transversion within codon 47 of the *No2* (nuclear opacity 2) mouse cataract. The sequence alteration is predicted to result in the nonconservative substitution of Ala for the normally encoded Asp (Steele *et al.,* 1998). A similar phenotype (microphthalmia and nuclear cataract) was observed in *Cx50* null mice (White *et al.,* 1998). A mutation in the corresponding human gene leads to a zonular pulverulent cataract (Shiels *et al.,* 1998) or nuclear cataract (Willoughby *et al.*, 2003). The Cx50-encoding gene *Gja8* is expressed mainly in lens fiber cells. However, Dahm *et al.,* (1999) showed that Cx50 (which is identical to the lens membrane protein MP70; White *et al.*, 1992) can also be found in the epithelial cells forming complexes with Cx43 (see below).

A knockout mutation of another type of connexin, the gene coding for connexin46 (or gap junction protein α3; gene symbol *Gja3*), exhibits nuclear cataract, which was associated with the proteolysis of crystallins. Obviously, there is no influence on the early stages of lens formation (Gong *et al.,* 1997). *Gja3* is mapped to mouse chromosome 14 (Haeflinger *et al.,* 1992). Recently, a novel mutation in human *GJA3* gene (TTC→TTA) results in a Phe→Leu substitution in the first transmembrane region of human connexin46. The mutation was proven to be causative for a congenital nuclear pulverulent cataract (Jiang *et al.*, 2003); however, a few years ago, Rees *et al.,* (2000) and Mackay *et al.,* (1999) showed also mutations in the human *GJA3* gene leading to zonular pulverulent cataracts. The two mutations affect different parts of the protein (the extra- and intracellular domain, resp.)

Similarly, disruption of the gene coding for connexin43 (gene symbol: *Gja1* for gap junction membrane channel protein α1) demonstrated normal development of the lens and differentiation of the fiber cells at the bow region. The lenses of the *Gja1*$^{-/-}$ mice exhibit grossly dilated extracellular spaces and intracellular vacuoles. These changes suggest that the osmotic balance within these cells is markedly altered (Gao and Spray 1998). *Gja1* is mapped to mouse chromosome 10 (29 cM from the centromere; Hsieh *et al.,* 1991). In agreement with the pleiotropic action of the gene, *Gja1* is expressed in very early mouse embryogenesis beginning in the blastocyst stage; later on, its expression is associated with many developmental processes involving the eye and otic vesicle, branchial arches, and migratory cells of the neural crest and sklerotomes (Paznekas *et al.*, 2003).

Mutations affecting the structural proteins of the lens cytosol

Up to 90% of the soluble protein in the postmitotic lens cells consists of proteins, which are referred to as α-, β-, and γ-crystallins (Mörner, 1893). The α-crystallins form high-molecular aggregates. Recent findings on the structure and function of α-crystallins demonstrated that they have chaperone activity and belong to the family of the small heat shock proteins. In contrast to αB-crystallin (gene symbol: *Cryab*), which is ubiquitously expressed, the αA-crystallin (gene symbol: *Cryaa*) occurs mainly in the lens. The β/γ-crystallin superfamily exhibits a characteristic protein motif, the so-called Greek key motif, in a quadruple organization. It is considered to be essential for the extremely high protein concentration within the lens (for reviews on crystallins see Wistow & Piatigorsky, 1988; Graw 1997; Bhat, 2003).

Moreover, because of the unique morphology of the lens fiber cells it is not surprising that also unique cytoskeletal proteins exist to be expressed more or less specifically in the lens. Among them, CP49 has to be mentioned, because its alteration leads to alterations of lens transparency. An overview and summary for all of these mutations is given in Table 2.

The α-crystallins

A few years ago, a knockout of the αA-crystallin-encoding gene *Cryaa*, was published; it leads to a recessive phenotype (Brady *et al.,* 1997). *Cryaa*$^{-/-}$ lenses develop an opacification that starts in the nucleus and progresses to a general opacification with age. Cataract formation is finally caused by insolubility of the αB-crystallin. *Cryaa* is mapped to mouse chromosome 17; cataract-causing mutations are referred to as *lop18* (recessive; Chang *et al.,* 1999) and *Aey7* (dominant; Graw *et al.*, 2001a). In contrast, knockout mice of *Cryab* encoding αB-crystallin are cataract-free, but they die prematurely because of myopathy and some other organ defects (Brady *et al.*, 2001). *Cryab* is mapped on mouse chromosome 9 (Xia *et al.,* 1996).

In human, one of the most common familial forms of congenital cataracts is referred to as the autosomal dominant congenital cataract (*ADCC*). An *ADCC* locus was mapped recently to human chromosome 21q22.3 near the αA-crystallin encoding gene, *CRYAA*. By sequencing this candidate gene, Litt *et al.,* (1998) found a missense mutation leading to an Arg→Cys exchange at the amino acid position 116, which is associated with *ADCC* in this family. Another mutation (R49C) leads to a similar dominant phenotype (Mackay *et al.*, 2003). In contrast to these two dominant phenotypes, Pras *et al.,* (2000) demonstrated a nonsense mutation (W9X) in *CRYAA* to be causative for an autosomal recessive cataract in an inbred Jewish Persian family.

Additionally, in human two different cataract-causing mutations have been described in *CRYAB*: at first, Vicart *et al.,* (1998) reported a dominant myopathy associated with cataract to be caused by a missense mutation (R120G). Subsequent *in vitro* studies demonstrated its defective chaperon-like function as the biochemical reason for formation of this particular type of cataract (Bova *et al.*, 1999). Later on, Berry *et al.,* (2001) reported another mutation in the human *CRYAB* gene causing dominant congenital cataract at the posterior pole of the lens. In a four-generation family of English descent, the authors mapped this type of cataract close to the *CRYAB* locus and found a deletion in exon 3 of *CRYAB* that resulted in a frameshift in codon 150 and an aberrant protein consisting of 184 residues. Because of these 35 new amino acids, this particular phenotype might be attributed to a dominant-negative function.

Since the α-crystallins belong to the family of small heat-shock proteins, it might be interesting to note that a mutation in a gene coding for heat-shock transcription factor 4 (gene symbol *HSF4*) is associated with a dominant, lamellar cataract (Bu *et al.*, 2002a)

The β-crystallins

The first cataract mutantation which was characterized on a molecular level was the so-called *Philly* mouse. It was demonstrated to be caused by an in-frame deletion of 12 bp in the βB2-crystallin encoding gene (*Crybb2*), resulting in a loss of four amino acids (Chambers and Russell, 1991). The region in which the deletion occurs is close to the carboxy-terminus and essential for the formation of the tertiary structure of the βB2-crystallin. The increasing severity of the phenotype is temporally correlated to the expression of the *Crybb2* gene (Carper *et al.*, 1982); *Crybb2* is mapped to mouse chromosome 5 (Kerscher *et al.*, 1995). After the 1st postnatal week, the characteristic bow configuration of the nuclei in the lens cortex was replaced by a fan-shaped configuration, and swelling of the lens fibers occurred (Uga *et al.*, 1980). Faint anterior opacities seen at postnatal day 15 are followed by sutural cataracts at day 25, nuclear cataract at 30 days, lamellar perinuclear opacities at 35 days, and total nuclear with anterior and posterior polar cataracts at 45 days. Cataractogenesis is associated with an intralenticular increase in water, sodium, and calcium, and a decrease in potassium, reduced glutathione, and ATP. An altered membrane permeability is the cause of an increased outward leak (Kador *et al.*, 1980). A similar phenotype (referred to as *Aey2*) was shown also to be caused by a mutation affecting the 4th Greek Key motif in the βB2-crystallin, however, in this case it was just an amino-acid exchange (Graw *et al.*, 2001c).

Also for these mouse mutations homologous diseases have been described in man; the first of them was referred to as cerulean cataract (*CCA2:* congenital cataract of cerulean type 2). This particular cataract is characterized by peripheral bluish and white opacifications in concentric layers with occasional central lesions arranged radially. Litt *et al.,* (1997) mapped this particular type of cataract to a region of human chromosome 22 containing three genes coding for different β-crystallins. Sequence analysis revealed that a chain-termination mutation in *CRYBB2* is associated with this particular type of cataract in this family. Moreover, it turned out that the same mutation was found in three independent families suffering from different types of cataracts. Detailed analysis demonstrated that a sequence-specific gene conversion between *CRYBB2* and its closely linked pseudogene is respon-

TABLE 2

MUTANT ALLELES CODING FOR CRYSTALLINS OR CYTOSKELETAL PROTEINS INVOLVED IN CONGENITAL CATARACTS

Name	*Allele Symbol*	Phenotype	Molecular lesion	Consequence for Protein	Reference
Cryaa	*Cryaa*$^{-/-}$	Recessive progressive opacity	Targeted deletion	Loss of function	Brady *et al.*, 1997
	lop18	Recessive nuclear and cortical cataract	R54H	n.d.	Chang *et al.*, 1999
	Aey7	Nuclear cataract	V124E	n.d.	Graw *et al.*, 2001a
CRYAA		Recessive cataract	W9X	Loss of function	Pras *et al.*, 2000
CRYAA		Dominant nuclear cataract	R49C	Abnormal nuclear localization	Mackay *et al.*, 2003
CRYAA		Dominant nuclear cataract	R116C	Increased membrane binding capacity	Cobb *et al.*, 2000
Cryab	*Cryaa*$^{-/-}$	No ocular phenotype	Targeted deletion	Loss of function	Brady *et al.*, 2001
CRYAB		Myopathy with cataract	R120G	Irregular structure	Vicart *et al.*, 1998; Bova *et al.*, 1999
		Posterior polar cataract	450delA	Aberrant protein	Berry *et al.*, 2001
Cryba1	*Po*	Progressive cataract	Splicing intron 6 W168R; ΔW168	4th Greek Key motif	Graw *et al.*, 1999
CRYBA1		Zonular cataract	Splicing intron 3	n.d.	Kannabiran *et al.*, 1998
CRYBA1		Pulverulent cataract	Splicing intron 3	n.d.	Bateman *et al.*, 2000
CRYBA1		Lamellar cataract	G91del	Reduced solubility	Qi *et al.*, 2004; Reddy *et al.*, 2004
CRYBA1		Cataract	Splicing intrin	n.d.	Burdon *et al.*, 2004
CRYBB1		Pulverulent cataract	G220X	Reduced solubility	Mackay *et al.*, 2002
Crybb2	*Philly*	Progressive cataract	12-bp deletion in exon 6	4th Greek Key motif	Chambers and Russell, 1991
	Aey2	Progressive cataract	V187E	4th Greek Key motif	Graw *et al.*, 2001c
CRYBB2		Cerulean cataract	Q155X	n.d.	Litt *et al.*, 1997
CRYBB2		Coppock-like cataract	Q155X	n.d.	Gill *et al.*, 2000
CRYBB2		Suture cataract and cerulean opacity	Q155X	n.d.	Vanita *et al.*, 2001
CRYBB2		Central nuclear cataract	W151C	Loss of solubility ?	Santhiya *et al.*, 2004
Cryga-f	*Several alleles in mouse*	Various types of cataract	Missense, nonsense, deletion/insertion	Mainly Greek Key motifs affected	See overview in Graw *et al.*, 2004*
CRYGC		Coppock-like cataract	T5P	Impairment of folding	Héon *et al.*, 1999
CRYGC		Zonular-pulverulent cataract	Insertion, 52 new amino acids	Hybrid protein	Ren *et al.*, 2000
CRYGC		Lamellar cataract	R168W	4th Greek Key motif	Santhiya *et al.*, 2002
CRYGD		Punctate progressive cataract	R14C	Altered surface properties	Stephan *et al.*, 1999
CRYGD		Lamellar cataract	P23T	n.d.	Santhiya *et al.*, 2002
CRYGD		Cerulean cataract	P23T	1st Greek Key Motif, altered folding & solubility	Nandrot *et al.*, 2003
CRYGD		Cataract	P23T	n.d.	Burdon *et al.*, 2004
CRYGD		Coral-shaped cataract	P23T	Less soluble	Mackay *et al.*, 2004
CRYGD		Fasciculiform cataract	P23T	n.d.	Shentu *et al.*, 2004
CRYGD		Prismatic crystals	R36C	crystallization	Kmoch *et al.*, 2000
CRYGD		Aculeiform cataract	R58H	Impairment of folding	Héon *et al.*, 1999
CRYGD		Central-nuclear	W158X	4th Greek Key motif	Santhiya *et al.*, 2002
Bfsp2	*Bfsp2*$^{-/-}$	Subtle loss of lens clarity	Targeted deletion	Loss of function	Alizadeh *et al.*, 2002; Sandilands *et al.*, 2003
	Dundee	Subtle loss of lens clarity	Splicing defect	Loss of function	Sandilands *et al.*, 2004
BFSP2		Juvenile onset cataract	R287W	Central rod domain	Conley *et al.*, 2000
		Nuclear cataract to spokelike opacity	ΔE233	Central rod domain	Jakobs *et al.*, 2000

n.d., not determined (or not reported); * In this reference, 20 mutations in mouse *Cryg* genes are discussed.

sible for this feature (Vanita *et al.*, 2001; Gill *et al.*, 2000). However, this does not explain the different cataract phenotypes.

Among the β-crystallin encoding genes, *Cryba1* is the second-most one affected by cataract-causing mutations. It codes for two β-crystallins, βA1- and βA3-crystallin, which differ by the length of their N-terminal extension (Peterson and Piatigorsky, 1986). In mouse, just one *Cryba1* mutation has been described (*progressive opacity*, *po*), which has a similar phenotype like the murine *Crybb2* mutations cited above (Graw *et al.*, 1999). Surprisingly, in human two independent mutations affect the same 5' (donor) splice site of intron 3: in the first case, it is a G→A transition (Kannabiran *et al.*, 1998), and in the second case a G→C transversion (Bateman *et al.*, 2000). Unfortunately, since human lens cDNA was not available, the novel splice product could not be characterized. The phenotype was described as zonular cataract with sutural opacity (Kannabiran *et al.*, 1998) or pulverulent, star-shaped or radial opacity (Bateman *et al.*, 2000). The third mutation was reported just recently (Reddy *et al.*, 2004) as a G91 deletion causing a lamellar cataract with variable severity in a five-generation family.

Another example of *CRYB* mutations concerns *CRYBB1*; in this gene a nonsense mutation (G220X) is associated with a fine, dustlike opacity affecting mainly the central zone of the lens (Mackay *et al.*, 2002).

The γ-crystallins

An intermediate member of the β/γ-crystallin superfamily is the γS-crystallin, previously also referred to as βS-crystallin. The corresponding gene *Crygs* was mapped to mouse chromosome 16 (Sinha *et al.,* 1998). The cataract mutation *opj* (*opacity due to poor juntions*) (Everett *et al.,* 1994; Kerscher *et al.,* 1996) was mapped close to *Crygs*. Sequence analysis of *Crygs* from *Opj* mice revealed a mutation coding for a key residue of the core of the N-terminal domain of the protein (Wistow *et al.,* 1998). Moreover, the first recessive mutation in mouse *Cryg* is characterized by a stop codon leading to a truncated protein that is missing 16 amino acids at the C terminus in the mouse *Crygs* gene (Bu *et al.*, 2002b).

The other six *Cryg* genes are organized as a cluster of very similar genes (*Cryga*->*Crygf*) within approximately 50 kb on mouse chromosome 1. In mice, mutations have been characterized affecting all of these 6 genes; however, it is apparent that *Cryge* has the highest mutation frequency. An overview about the 20 characterized mouse mutants has been published recently (Graw *et al.*, 2004). The first mutant, which was identified in this field is the *Elo* mutant (*Eye lens obsolescence;* Oda *et al.*, 1980*)*; it was characterized by a single nucleotide deletion in the *Cryge* gene. The mutation destroys the reading frame of the gene, and at the protein level one of the Greek key motifs is affected (Cartier *et al.,* 1992). Therefore, the new allele symbol is *Cryge* ^{elo}. One of the cataract mutants being most characterized among this group was originally referred to as *Nop* (*nuclear opacity*). It was of spontaneous origin (Graw *et al.*, 1984) and shown to be caused by a small deletion of 11 bp and an insertion of 4 bp in the 3rd exon of the *Crygb* gene (novel allele symbol: *Crygb* ^{nop}*)*. It leads to a frame shift and creates finally a new stop codon; the corresponding γB-crystallin protein is predicted to be truncated after 144 amino acids; the last six amino acids are different from the wild-type γB-crystallin. Western blot analysis demonstrated the stable expression of the wrong protein (Klopp *et al.*, 1998).

Using *in situ* hybridization techniques with a probe detecting all *Cryg* transcripts in embryonic sections, a lower extent of *Cryg* transcripts was detected in the *Crygb* ^{nop} mutants beginning from embryonic day 13.5. The first morphological abnormality in the mutant lenses was observed as swelling of lens fibers at embryonic day 15.5 (Santhiya *et al.*, 1995).

The nuclei of the cortical cells could also be detected in the area of the lens nucleus of the *Crygb* ^{nop} and *Cryge* ^{t} lenses (Graw *et al.*, 1990a; 1990c). Biochemical investigations demonstrated an increase in the concentration of oxidized glutathione in the *Crygb* ^{nop} lenses over the wild type, which is not due to a corresponding decrease of an enzyme related to this metabolite (Graw *et al.*, 1985; 1989).

All these *Cryg* mutations affect only the lens cells and no other part of the eye; however, the size of the entire eye is always smaller than the wild type. A common feature in three mutants investigated is the inhibition of a Mg^{2+}-dependent DNase in the lens. The decrease of DNase activity followed the same directionality (*Cryge* ^{ns}>*Crygb* ^{nop}>*Cryge* ^{t}) as the decrease in the relative content of water-soluble lens protein, which might be used as a rough indicator for the severity of cataractogenesis (Graw and Liebstein, 1993). Although *Cryg*-mutation mediated mechanisms of cataract formation are not yet fully understood, it is known that the mutations interfere with the breakdown of the lens fibre cell nuclei during terminal differentiation. The alteration of this process was recently demonstrated for three mouse *Cryg* mutants - *Crygb* ^{nop}, *Cryge* ^{elo}, *Cryge* ^{t} - in which it was shown that ultimately the mutant γ-crystallins contribute to the formation of amyloid-like fibers in the lens fiber cell nuclei (Sandilands *et al.*, 2002).

Some of the inherited cataracts in man are also related to mutations in the crystallin-encoding genes. In humans, two of the six *CRYG* genes on chromosome 2 are pseudogenes (Brakenhoff *et al.*, 1994). The list of families with hereditary congenital dominant cataracts who carry mutations in the *CRYG* genes is growing rapidly (see Table 2). Mutations associated with a clinical phenotype have been found up to now only in *CRYGC* and *CRYGD*. There appear two remarkable features: first, the *CRYGD*-P23T mutation was observed in five independent families from different continents and reported to be causative for phenotypically diverse cataractous features. It is obviously no SNP or common polymorphism, because some of the studies looked for this mutations not only in the healthy relatives, but also in 100 unaffected people. It might be somehow dependant on the sequence, because the wild-type sequence CCACCCCAA changes to CCACACCAA. The second point of interest is that one of the dominant human *CRYGD* mutations (W156X) is identical to the dominant mouse *Lop12* mutation (Smith *et al.*, 2000). In this case, 18 amino acids are missing at the C-terminus and lead to a dominant phenotype (in contrast to the 16 amino acids that are missing in the γS-crystallin, which lead to a recessive phenotype). The common single base-pair exchange is G→A, which cannot be explained by a slippage mechanism during DNA replication.

Cytoskeletal proteins

Among the lens cytoskeletal proteins filensin, vimentin and CP49 (also referred to as phakinin or beaded filament structural protein 2), the CP49 seems to be very important for the lens, because it is the only one among these three, which is sensitive to the deletion or mutation of its gene (at least with respect for

cataract formation). CP49 and filensin, together with α-crystallins, have been shown to immunolocalize to unique cytoskeletal structures within the lens fiber cells known as beaded filaments. They are considered to be important in facilitating the chaperone activity of α-crystallin assemblies. Mutations in CP49-encoding gene *BFSP2* were shown to be responsible for dominant cataracts in human (Conley *et al.*, 2000, Jakobs *et al.*, 2000); their phenotypes, however, seem to be variable ranging from congenital nuclear, sutural or stellate cataracts to juvenile-onset cataracts.

In the mouse, the knockout of the corresponding gene does not lead to cataracts, even if the absence of CP49 causes a subtle loss of optical clarity in the lens (Alizadeh *et al.*, 2002; Sandilands *et al.*, 2003). Moreover, a deletion of the splice-acceptor site in exon 2 of the mouse *Bfsp2* results in a splicing of exon 1 to exon 3 and causes a frameshift in the reading frame as well as the introduction of a stop codon at position 2 of exon 3 in the *Bfsp2* transcript. The phenotype of this mutation is also subtle as described for the knockout of the entire gene. Since this mutation is present in several mouse strains (129, 101 and CBA), it might interfere with other mutations or targeted deletions and, therefore, it might have important implications for lens studies using these strains (Sandilands *et al.*, 2004).

Further congenital cataracts

Hyperferritinaemia and I/i-antigens

Hereditary hyperferritinaemia-cataract syndrome (HHCS; OMIM #600886) is a rare autosomal dominant condition identified by high serum ferritin levels with normal iron saturation and distinctive bilateral cataract. The elevated serum ferritin is due to various mutations in the iron-responsive element (IRE) of the *l-ferritin* gene, resulting in excessive l-ferritin production. The IRE in the ferritin mRNAs is a hairpin structure near the beginning of the 5'-untranslated region. Trans-acting iron-regulatory proteins bind this RNA element and decrease ferritin translation by competing for ribosome binding. An increase in iron decreases the binding of these proteins, relieving inhibition of ferritin mRNA translation and resulting in increased ferritin mRNA translation. Mutations in this structure interefer with this IRE-mediated regulation of ferritin synthesis and lead to persistent hyperferritinemia (Brooks *et al.*, 2002).

The first reports concerning this topic started in 1995 (Beaumont *et al.*, 1995; Girelli *et al.*, 1995). In the meantime, further papers have been published (surprisingly, most of them came from Northern Italy, a few from other European countries, and one from Australia) demonstrating a variety of onset, severity and type of cataracts caused by these mutations. The onset of this type of cataract is in some cases also early in childhood, and therefore, this syndrome should be suspected and ferritin levels measured in all cases of cataract in children (Campagnoli *et al.*, 2002). However, other genetic causes for hyperferritinaemia (like mutations in the gene coding for ferroportin) are not associated with cataracts (Cazzola *et al.*, 2002). Actually, there is no mouse model available.

Just recently, it was reported that congenital cataracts might be associated with the adult *i* phenotype, which can be observed in healthy people only at the surface of fetal or neonatal red blood cells. The human i and I antigens are characterized as linear and branched repeats of N-acetyllactosamine, respectively. Conversion of the i to the I structure requires I-branching beta-1,6-N-acetylglucosaminyltransferase activity. It has been noted that the null phenotype of *I*, the adult *i* phenotype, is associated with congenital cataracts mainly in Asians. The results suggest a molecular genetic mechanism that may explain the partial association of the adult *i* phenotype with congenital cataracts and indicate that a defect in the *I* locus may lead directly to the development of congenital cataracts (Yu *et al.*, 2003).

Mutants waiting for molecular characterization

Besides the *Mip/aquaporin* cataracts, another group of cataract mutations is localized at mouse chromosome 10, in this case 3.2 cM proximal to *Si* (Löster *et al.*, 1997). It consists of two alleles and is provisionally referred to as *Cat3* (Kratochvilova and Favor, 1992). *Cat3^{vl}* (vacuolated lens; Kratochvilova, 1981) and *Cat3^{vao}* (cataract with anterior opacity; Graw *et al.*, 1986) arose independently in the F_1 generation after paternal γ-irradiation. On the basis of the location of *Cat3* to this defined region of chromosome 10, several genes have been considered as candidates for *Cat3*, but none of them was confirmed as target of the mutations (Löster *et al.*, 1997). To the region of conserved synteny at human chromosome 12q21-24 the human eye disorder *cornea plana congenita* has been mapped and shown to be caused by mutations in *KERA*, coding for keratocan (Pellegata *et al.*, 2000).

Slit lamp observation revealed that the lenses of the *Cat3^{vl}* mutants are filled up with small and large vacuoles. Pupillary dilatation is limited. The anterior chamber is flattened, and opacified corneas are frequently observed. The *Cat3^{vao}* mutants show an opaque area immediately beneath the lenticular capsule forming multiple disk-like opacities around the optical axis. The two alleles differ mainly in the appearance of their opacities (Löster *et al.*, 1997).

The histological analysis identified an aberrant cell layer between the anterior epithelium and the primary lens fibers at embryonic day E12.5, when the lens vesicle is filled by the primary lens fibers. It leads to a maldevelopment of the anterior lens epithelium and degeneration of the fibers. After birth, the lens capsule ruptures at the equatorial region, and synechiae with the iris occur (Graw, 1999). Biochemical examination of the cataractous *Cat3^{vao}* lenses demonstrated the presence of oxidative and osmotic stress (Graw *et al.*, 1989; 1990b).

The dominant X-linked cataract mutation *Xcat* was recovered after parental radiation (Favor and Pretsch, 1990). Histological analysis during the embryonic development revealed that in the affected embryos the primary fiber cells are irregularly arranged and show small foci of cellular disintegration. Progressive degeneration of fibers occurs. However, the lens epithelium and the newly differentiated fibers show no evident abnormality indicating that the mutation affects the differentiation of the primary lens fiber cells after their initial elongation. Analysis of crystallin and cytoskeleton proteins of postnatal cataractous lenses revealed no significant abnormalities when compared to the normal lens (Grimes *et al.,* 1993). Detailed genetical analysis placed the *Xcat* mutation to the distal end of the mouse X chromosome. It suggests that this locus should map to a conserved block at Xp22.1-p22.3 in human. To this region, the Nance Horan Syndrome (NHS) has been mapped but the corresponding gene has been excluded as candidate (Stambolian *et al.*, 1994) as well as

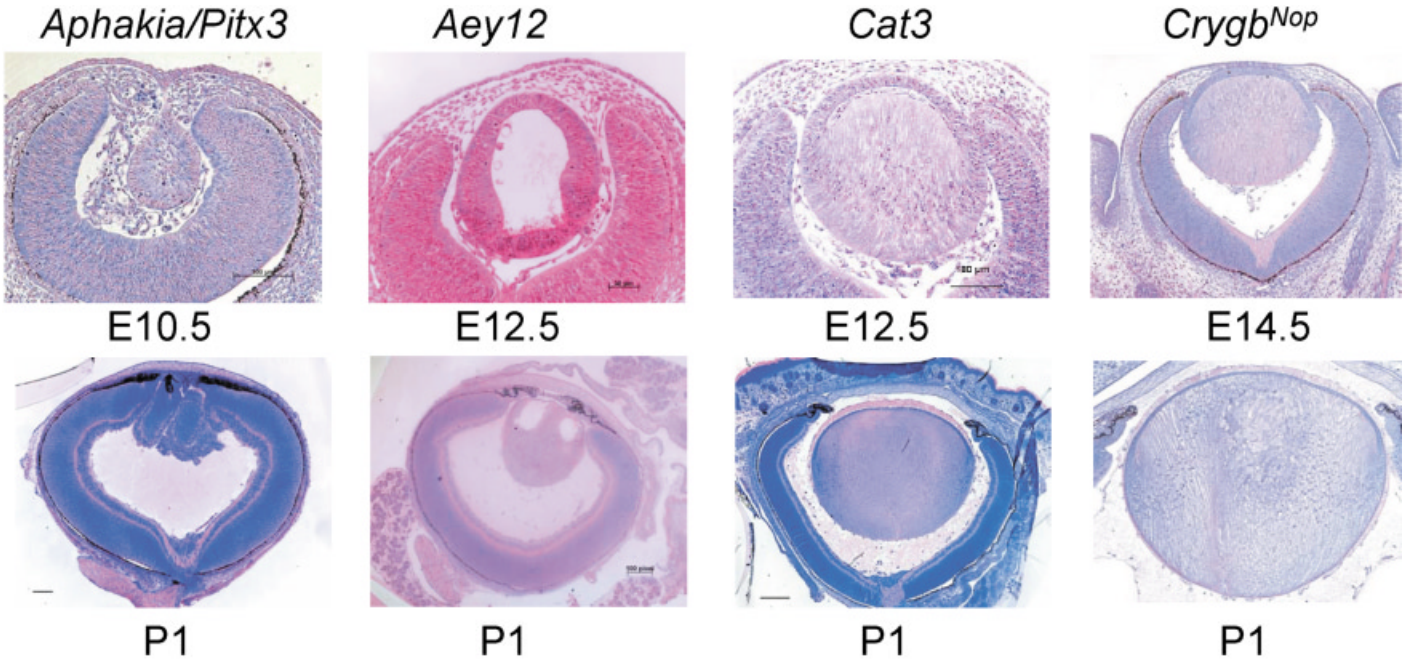

Fig. 2. Overview on mutations affecting early development. *Four different mutants are presented, which affect eye and lens development at different embryonic time points (E); for later comparison, in all cases neonatal eyes are shown: The* aphakia/Pitx3 *mutation stops eye development at the lens stalk stage, and leads finally to an overgrowth of the retina because of missing inhibitory signals from the lens; the unknown mutation in the* Aey12 *stops lens development at the lens vesicle stage; retina differentiation is poor, and the iris covers the entire anterior segment; the unknown* Cat3 *mutation interferes with the secondary lens fiber cell differentiation and leads to vacuolisation of the lens; however, the retina differentiation is not affected; the* Crgyb *mutation* Nop *affects late lens development; there is no obvious defect in other ocular tissues.*

some others (Zhou *et al.*, 1995) Moreover, Francis *et al.,* (2002) mapped an isolated cataract in man to the same chromosomal region.

Another X-linked mouse mutant with affected lenses is referred to as *bare patches* (*Bpa*). Since hemizygous males die before birth, heterozygous females have patches of bare skin. Lens cortical "frost figure" opacities are present. *Bpa* is considered as a model for human X-linked syndrome chondrodysplasia punctata (Happle *et al.*, 1983; Angel *et al.*, 1993).

The mutation *vacuolated lens* (*vl*) is mapped to mouse chromosome 1 and leads to opaque white lenses. Additionally, the mutants are characterized by a white belly spot and *spina bifida*. Small lens vacuoles are present at birth (Dickie, 1967; 1969). The mutant *blind-sterile* (*bs*) is characterized by bilateral nuclear cataracts, microphthalmia and glossy coats. The cataracts are detectable at E16. Females are fertile, but males are sterile. The mutation was mapped to mouse chromosome 2 (Varnum, 1983).

The *Tcm* mutation (total cataract with microphthalmia), a cataract with iris dysplasia and coloboma (Zhou *et al.*, 1997) and the *Ccw* mutation, *cataract and curly whiskers* (Kerscher *et al.,* 1996), are localized on mouse chromosome 4. The *nuclear-posterior polar opacity* (*Npp*) maps to chromosome 5, and *Cat5* (*previously To2*), a total opacity, to chromosome 10 (Everett *et al.*, 1994).

The so-called *rupture of lens cataract* (*rlc*) was mapped to chromosome 14 (Matsushima *et al.*, 1996) and a similar form, *lr2* (*lens rupture 2*) was mapped to a close position (Song *et al.*, 1997). The opacity in the *rld rlc* mice becomes apparent at 35-60 days of age; there are no developmental changes reported (Iida *et al.*, 1997). Another form of cataracts, which is formed postnatally without observed developmental alterations, is the *Nakano cataract* (*nct*; Takehana, 1990; Wada *et al.*, 1991). The mutation was mapped to chromosome 16 (Hiai *et al.*, 1998).

Conclusion and perspectives

A great variety of mouse mutants affecting ocular development is available. They arose spontaneously, or were recovered after parental treatment by chemical mutagens or radiation. Recent development of molecular methods is leading to a rapidly increasing number of transgenic mice overexpressing particular genes in distinct tissues or representing null alleles by targeted disruption of the genes. The molecular analysis of the affected genes together with the detailed phenotypical analysis, will allow us to understand the pathways of ocular development.

A first set of mutants might indicate the inverse relationship between lens and retina development. Fig. 2 shows four examples of mouse mutants with different onsets of morphological alterations in the lens starting with the *aphakia* mouse and its arresst at the lens stalk stage. In this case, the growth of the retina is obviously not limited, and after birth, retinal tissues fills the entire eye ball. In contrast, mutations affecting the *Cryg* genes affect the lens severely, however, the retina remains unaffected. The two other mutants with their major defects are laying between these two extremes – the *Aey12* mutants with their arrest at the lens vesicle stage (Graw *et al.*, 2003) or the *Cat3* mutants with their problems in the initial phase of the secondary fiber cell formation (Löster *et al.*, 1997) – have obviously smaller consequences for the retina development than the *aphakia* mouse.

The more detailed analysis of these mutants will enable us to describe also more precisely the mechanisms leading to the

pathological situation. The mouse as one of the most important model systems in eye development is currently be supplemented by the rapidly increasing number of mutants in the zebrafish (Glass and Dahm, 2004). Together with modern techniques in biochemistry, it might become possible in the near future to treat at least some of the inherited ocular diseases either by novel drugs or by somatic gene therapy. For each of these steps, mouse mutants are an indispensible tool.

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