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SCIENCE DIRECT
Experimental Eye Research 81 (2005) 503–512
EXPERIMENTAL EYE RESEARCH
www.elsevier.com/locate/yexer

Review

Mouse mutants as models for congenital retinal disorders

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Received 1 February 2005; accepted in revised form 1 June 2005
Available online 18 July 2005

Abstract

Animal models provide a valuable tool for investigating the genetic basis and the pathophysiology of human diseases, and to evaluate therapeutic treatments. To study congenital retinal disorders, mouse mutants have become the most important model organism. Here we review some mouse models, which are related to hereditary disorders (mostly congenital) including retinitis pigmentosa, Leber's congenital amaurosis, macular disorders and optic atrophy.

Keywords: animal model; retina; mouse; gene mutation; retinal degeneration

1. Introduction

Mice suffering from hereditary eye defects (and in particular from retinal degenerations) have been collected since decades (Keeler, 1924). They allow the study of molecular and histological development of retinal degenerations and to characterize the genetic basis underlying retinal dysfunction and degeneration. The recent progress of genomic approaches has added increasing numbers of such models.

In recent years systematic phenotype-driven approaches have been developed to screen for mice harboring chemically induced mutations, mainly by use of N-ethyl-N-nitrosourea (ENU), which predominantly causes point mutations (Justice et al., 1999). Moreover, many transgenic and knockout animal models were created to investigate the role of specific genes on retinal function. Finally, the gene-trapping method was developed for the systematic generation of knockout mice (Skarnes et al., 2004).

Although mouse models are a good tool to investigate retinal disorders, one should keep in mind that the mouse retina is somehow different from a human retina, particularly with respect to the number and distribution of the photoreceptor cells. The mouse as a nocturnal animal has a retina dominated by rods; in contrast, cones are small in size and represent only 3–5% of the photoreceptors. Mice do not form cone-rich areas like the human fovea. Instead of three cone pigments present in the human retina, mice express only two distinct pigments with absorption maxima near 350 and 510 nm (Lyubarsky et al., 1999).

In this review we discuss important mouse mutants for retinal degenerations (for cross information on their mutated genes and chromosomal localization see Table 1 and Fig. 1). Concerning the nomenclature of genes and mutations, we follow the mouse genetic nomenclature as outlined by the Jackson Laboratory (http://www.informatics.jax.org).

1.1. Retinal disorders including degeneration of photoreceptor cells

1.1.1. Models for retinitis pigmentosa (RP)

One of the first mouse mutants described in the field of vision research was the *rodless* mouse (*r*; Keeler, 1924), which carries a nonsense mutation in the *Pde6b* gene coding for the β-subunit of phosphodiesterase. The gene mutation was later discovered in the *retinal degeneration* mouse (actual gene symbol $Pde6b^{rd1}$, formerly referred to as *rd1* or *rd*; Pittler and Baehr, 1991). A viral insertion in intron 1 of the $Pde6b^{rd1}$ allele (Bowes et al., 1993) coding for

Abbreviations BBS, Bardet-Biedl syndrome; ENU, N-ethyl-N-nitrosourea; ERG, electroretinogram; LCA, Leber's congenital amaurosis; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; STGD, Stargardt's macular dystrophy.

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doi:10.1016/j.exer.2005.06.004

Table 1
Overview of mutations in the mouse, affecting the structure or function of the retina. For allelic series just a few examples are listed

Gene Symbol	Chr. (cM)	Defect alleles	Mutation	Reference
Crb1 *crumbs homolog 1 (Drosophila)*	1 (73.0)	*Crb1*^{rd8}	1 bp deletion causing a frame shift and premature stop codon	Mehalow et al., 2003
		Crb1^{tm1Wij}	Knockout, insertion of a hygromycin resistance cassette the promoter region, exon 1 and part of intron 1	van de Pavert et al., 2004
Cnga3 *cyclic nucleotide gated channel alpha 3*	1 cyto-band B	*Cnga3*^{tm1Biel}	Knockout, the gene was disrupted by replacement of exon 7 with a neomycin resistance cassette	Biel et al., 1999
Vsx1 *visual system homeobox 1 homolog (zebrafish)*	2 (83.9)	*Vsx1*^{tm1Bhr}	Knockout, a neo cassette replacing the coding region for the entire homeodomain and CVC domain	Ohtoshi et al., 2004
		Vsx1^{tm1Mci}	Knockout, a genomic fragment, was replaced with a neomycin selection cassette inserted by homologous recombination	Chow et al., 2004
Abca4 *ATP-binding cassette, sub-family A (ABC1), member 4*	3 (61.8)	*Abca4*^{tm1Ght}	Knockout, replacement of a 4 kb genomic fragment containing the promoter and first exon with a neomycin cassette	Weng et al., 1999
Rpe65 *retinal pigment epithelium 65*	3 (87.6)	*Rpe65*^{tm1Tmr}	Knockout, exons 1–3 of the gene were replaced with a PGK-neo cassette	Redmond et al., 1998
		Rpe65^{rd12} (retinal degeneration 12)	Nonsense mutation, base substitution (C to T) in codon 44	Pang et al., 2005
Pde6b *rod phospodiesterase, beta subunit (r,rodless; rd, retinal degeneration)*	5 (57.0)	*Pde6b*^{rd1} (retinal degeneration 1)	Nonsense mutation, C-A transversion in codon 347 (exon 7)	Pittler and Baehr, 1991
		Pde6b^{rd10} (retinal degeneration 10)	Missense mutation in exon 13	Chang et al., 2002
		Pde6b^{2J} 2 Jackson	Point mutation in exon 16	
		Pde6b^{atrd2} atypical retinal degeneration 2	ENU induced	Thaung et al., 2002
Mitf *microphthalmia-associated transcription factor*	6 (40.0)	*Mitf*$^{mi-sp}$ microphthalmia spotted	Insertion of an extra C residue in the poly-pyrimidine tract located upstream of an 18 bp alternative exon	Steingrimsson et al., 1994
		Mitf^{mi-vit} vitiligo	G to A transition at bp 793 that leads to an aspartate to asparagine substitution	Steingrimsson et al., 1994
		Mitf^{Mi-wh} microphthalmia white	T to A transversion at bp 764, which leads to an isoleucine to asparagine substitution	Steingrimsson et al., 1994
Rho *rhodopsin*	6 (51.5)	*Rho*^{tm1Jlem}	Knockout, a PGK-neo cassette was inserted into the first coding exon	Lem et al., 1999
		Rho^{tm1Phm}	Knockout, a neomycin cassette under the control of a polymerase II promoter was inserted at codon 135 in exon 2	Humphries et al., 1997
Crx *cone-rod homeobox containing gene*	7 (8.5)	*Crx*^{tm1Clc}	Knockout, the homeodomain coding region containing exon 3 and a portion of exon 4 was replaced by a neomycin selection cassette	Furukawa et al., 1999
Tub *tubby candidate gene*	7 (51.4)	*Tub*$^{tub-rd5}$	G to T transversion resulting in a larger transcript	Noben-Trauth et al., 1996
		Tub^{tm1Rok}	Knockout, a neomycin cassette replaced 16 kb of sequence spanning exons 1–8	Stubdal et al., 2000
Cln8 *ceroid-lipofuscinosis, neuronal 8*	8 (6.0)	*Cln8*^{mnd}*(motor neuron degeneration)*	A single nucleotide insertion (267-268C, codon 90) predicts a frameshift and a truncated protein	Ranta et al., 1999
nr nervous	8 (8.0)	*nr*	spontaneous	De Jager et al., 1998
Bbs2 *Bardet-Biedl syndrome 2 homolog (human)*	8 syntenic	*Bbs2*^{tm1Vcs}	Knockout, exons 5–13 were replaced with a neo	Nishimura et al., 2004
Mfrp *membrane-type frizzled-related protein*	9 (25.5)	*Mfrp*^{rd6}	4 bp deletion in the splice donor sequence of intron 4 - skipping of exon 4 (no frame shift)	Kameya et al., 2002
Bbs4 *Bardet-Biedl syndrome 4 homolog (human)*	9 (33.0)	*Bbs4*^{Gt1Nk}	A gene trap vector was inserted into intron 1, causing aberrant splicing	Kulaga et al., 2004
		Bbs4^{tm1Vcs}	Exons 6–11 were replaced with a neo cassette	Mykytyn et al., 2004

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