



## Shedding light on myopia by studying complete congenital stationary night blindness

Christina Zeitz, Jérôme E Roger, Isabelle Audo, Christelle Michiels, Nuria Sánchez-Farías, Juliette Varin, Helen Frederiksen, Baptiste Wilmet, Jacques Callebert, Marie-Laure Gimenez, et al.

### ► To cite this version:

Christina Zeitz, Jérôme E Roger, Isabelle Audo, Christelle Michiels, Nuria Sánchez-Farías, et al.. Shedding light on myopia by studying complete congenital stationary night blindness. Progress in Retinal and Eye Research, 2023, 10.1016/j.preteyeres.2022.101155 . hal-03954516

**HAL Id: hal-03954516**

**<https://cnrs.hal.science/hal-03954516>**

Submitted on 31 Jan 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**TITLE**

**Shedding light on myopia by studying complete congenital stationary night blindness**

Christina Zeitz a,\*, Jérôme E. Roger b, Isabelle Audo a,c, Christelle Michiels a, Nuria Sánchez-Farías a,1, Juliette Varin a,1, Helen Frederiksen a, Baptiste Wilmet a, Jacques Callebert d, Marie-Laure Gimenez a, Nassima Bouzidi a, Frederic Blond a, Xavier Guillonneau a, Stéphane Fouquet a, Thierry Léveillard a, Vasily Smirnov a, Ajoy Vincent e,f,g, Elise H2on e,f,g, José-Alain Sahel a,c,h, Barbara Kloeckener-Gruissem i, Florian Sennlaub a, Catherine W. Morgans j, Robert M. Duvoisin j, Andrei V. Tkatchenko k,l, Serge Picaud

a Sorbonne Université, INSERM, CNRS, Institut de la Vision, Paris, France

b Paris-Saclay Institute of Neuroscience, CERTO-Retina France, CNRS, Université Paris-Saclay, Saclay, France

c CHNO des Quinze-Vingts, INSERM-DGOS CIC 1423, Paris, France

d Service of Biochemistry and Molecular Biology, INSERM U942, Hôpital Lariboisière, APHP, Paris, France

e Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, ON, Canada

f Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada

g Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada

h Department of Ophthalmology, The University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

i Department of Biology, ETH Zurich, Zurich, Switzerland

j Department of Chemical Physiology & Biochemistry, Oregon Health & Science University, Portland, OR, USA

k Oujiang Laboratory, Zhejiang Laboratory for Regenerative Medicine, Vision and Brain Health, Wenzhou, China

l Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University, New York, NY, USA

## Abstract

Myopia is the most common eye disorder, caused by heterogeneous genetic and environmental factors. Rare progressive and stationary inherited retinal disorders are often associated with high myopia. Genes implicated in myopia encode proteins involved in a variety of biological processes including eye morphogenesis, extracellular matrix organization, visual perception, circadian rhythms, and retinal signaling. Differentially expressed genes (DEGs) identified in animal models mimicking myopia are helpful in suggesting candidate genes implicated in human myopia. Complete congenital stationary night blindness (cCSNB) in humans and animal models represents an ON-bipolar cell signal transmission defect and is also associated with high myopia. Thus, it represents also an interesting model to identify myopia-related genes, as well as disease mechanisms. While the origin of night blindness is molecularly well established, further research is needed to elucidate the mechanisms of myopia development in subjects with cCSNB. Using whole transcriptome analysis on three different mouse models of cCSNB (in *Gpr179*<sup>-/-</sup>, *Lrit3*<sup>-/-</sup> and *Grm6*<sup>-/-</sup>), we identified novel actors of the retinal signaling cascade, which are also novel candidate genes for myopia. Meta-analysis of our transcriptomic data with published transcriptomic databases and genome-wide association studies from myopia cases led us to propose new biological/cellular processes/mechanisms potentially at the origin of myopia in cCSNB subjects. The results provide a foundation to guide the development of pharmacological myopia therapies.

76	<b>Keywords:</b> congenital stationary night blindness, myopia, retina, transcriptome sequencing,
77	meta-analysis
78	
79	Contents
80	1. Introduction
81	2. Phenotype in human cases and animal models with complete congenital stationary night
82	blindness (cCSNB) and associated myopia
83	2.1. Signal transmission from photoreceptors to ON-bipolar cells
84	2.2. Visual acuity in cCSNB and myopia
85	2.3. Retinal structure in cCSNB and myopia
86	3. Studying myopia in mouse models
87	4. Differentially expressed genes in cCSNB
88	4.1. RNA-Seq studies in mouse models for cCSNB
89	4.2 Validation of RNA-Seq studies
90	4.3. Known genes implicated in CSNB
91	4.4. Transcriptome analyses of DEGs in cCSNB
92	4.4.1. Single cell analyses of DEGs in subpopulation of bipolar cells
93	4.5. Pathway analyses of DEGs involved in CSNB and correlation with myopia
94	4.5.1. MAPK pathway
95	4.5.2. Synapse
96	4.5.3 GPCR ligand binding
97	4.5.4 Eye, endoderm, and connective tissue development
98	4.5.5. Genes not associated to any pathway, unknown function and limited amount of
99	expression in the retina
100	4.5.6 Other genes from myopia databases that are differentially regulated in at least one
101	mouse model with cCSNB

5. Cause of reduced expression of many DEGs in cCSNB

6. Future perspectives

6.1. Identification of differentially expressed genes in cCSNB models using a whole

transcriptomic approach may yield novel proteins important for retinal signaling, as well as

novel myopia-related genes

6.2. Retinal expression of DEGs, pathway analyses and correlation to eye phenotypes

6.3 Novel candidate genes important for vision

6.4 Treatment of cCSNB and myopia

6.4.1 Pharmacological myopia treatment

Acknowledgments

References

Figures legends

## 1. Introduction

**Myopia** (short-sightedness) is the most common human eye disorder worldwide, in which the image is focused in front of the retina, resulting usually from an excessive growth of the eye posterior segment (increased axial length) (reviewed by e.g. (Goss and Wickham, 1995; McBrien and Gentle, 2003), generally as a consequence of accelerated post-natal eye growth (McBrien and Gentle, 2003) but also set by the optical power of the cornea and the lens (Iribarren, 2015). It can be due to structural abnormalities of the cornea as found in keratoconus or due to changes primarily in the lens power found e.g. in older people developing cataracts (reviewed by (Flitcroft et al., 2019; Iribarren, 2015)). Recent animal studies, combined with clinical studies, have revealed that the mechanisms of optically guided eye growth are influenced by the retina (Flitcroft, 2012).

**High axial myopia**, defined as a refractive error of more than  $-6.0$  diopters (D) or ocular axial length of more than 26–26.5 mm (Flitcroft et al., 2019), can lead to blinding complication such as myopic macular degeneration (MMD), retinal tears and retinal detachment, and predispose to other ocular diseases such as glaucoma and early onset cataracts (Hornbeak and Young, 2009). A subset of subjects with high myopia also demonstrate diffuse retinal changes beyond the macula, so-called “diffuse chorioretinal atrophy”, which is defined as **pathologic myopia** (Ohno-Matsui et al., 2016); pathologic myopia can be associated with fundus changes, regional retinal and choroidal thinning (Ohno-Matsui and Jonas, 2019; Ye et al., 2019), and increased retinal complications, such as retinal detachment (Ohno-Matsui et al., 2016). Epidemiological studies estimated that half the world’s population will be myopic by 2050, with **10% showing high myopia** (Holden et al., 2016). Indeed, it was shown that the incidence of myopia is increasing, affecting now 20%-

165 40% of children at the age of 17-18 in **developed western countries** and up to 80% -90% in  
166 **East and Southeast Asia** (reviewed by (Morgan et al., 2018) (e.g.(Ang et al., 2020;  
167 Cumberland et al., 2015; Foster and Jiang, 2014; French et al., 2013; Holden et al., 2014;  
168 Holden et al., 2016; Hysi et al., 2014; Kempen et al., 2004; Lam et al., 2004; Lin et al., 2004;  
169 Morgan et al., 2018; Morgan et al., 2012; Pan et al., 2012; Vitale et al., 2009)). However, in  
170 **less developed countries, with less developed education systems**, the prevalence of myopia  
171 in young adults is estimated to be only 5% -10% (reviewed by (Morgan et al., 2018) (e.g.  
172 (Anera et al., 2009; Casson et al., 2012; Dandona et al., 2002a; Dandona et al., 2002b; Gao et  
173 al., 2012; Jimenez et al., 2004; Jimenez et al., 2012; Khandekar and Abdu-Helmi, 2004;  
174 Lewallen et al., 1995; Lindquist et al., 2011; Lithander, 1999; Pokharel et al., 2000)).

175 High myopia is a complex disorder, which is mediated by genetic and more importantly by  
176 environmental factors (Baird et al., 2010; Morgan and Rose, 2005; Morgan, 2003; Morgan et  
177 al., 2018; Wojciechowski, 2011; Young, 2009). More than 300 genes were associated with  
178 refractive error development in humans (Flitcroft et al., 2018; Hysi et al., 2020; Kiefer et al.,  
179 2013; Tedja et al., 2019; Tedja et al., 2018; Verhoeven et al., 2013). They encode proteins of  
180 vastly different functions, including **eye morphogenesis, extracellular matrix organization,**  
181 **visual perception, circadian rhythms, pigmentation and retinal signaling** (Flitcroft et al.,  
182 2018; Hysi et al., 2020; Tedja et al., 2018). The contribution of heritability to myopia is  
183 difficult to determine (Dirani et al., 2006; Hammond et al., 2001; Lopes et al., 2009; Lyhne et  
184 al., 2001; Peet et al., 2007; Tedja et al., 2019; Tedja et al., 2018; Teikari et al., 1988;  
185 Wojciechowski, 2011) and estimated to be rather low (Morgan and Rose, 2005), since it was  
186 shown that environmental factors play a very important role in the occurrence of myopia,  
187 especially illumination conditions. This is underpinned by the increasing prevalence of  
188 myopia taking place in East and Southeast Asia, where children spend more time inside  
189 studying as compared to less developed countries (Morgan et al., 2018).

Indeed, the intensity of ambient **light** was found to influence the development of myopia. **Outdoor activities have a protective effect against the development and progression of myopia** (He et al., 2015; Rose et al., 2008; Wu et al., 2013; Xiong et al., 2017). Similarly for animal models raised under different lighting conditions, high illuminances have been found to slow the development of induced myopia (Smith et al., 2012). Interestingly, intermittent exposure to bright light was more efficient in suppressing myopia progression than continuous light exposure (Lan et al., 2014).

The identification of differentially expressed genes (DEG) in animals with induced myopia has been helpful in suggesting candidate genes associated with the development of human myopia (Brand et al., 2007; Frost and Norton, 2012; Gao et al., 2011; McGlinn et al., 2007; Riddell et al., 2016; Schippert et al., 2008; Shelton et al., 2008; Siegwart and Norton, 2002; Tkatchenko et al., 2016; Tkatchenko et al., 2006).

**High myopia can also be syndromic. Pathogenic variants affecting proteins** expressed in the retina, either in **photoreceptors** or in the downstream **bipolar cells (BCs)** can lead to progressive and non-progressive retinal monogenetic disorders, which can be also associated with other ocular disorders including **myopia**. One such disease is X-linked retinitis pigmentosa (RP) (MIM #300029), one of the most frequent and severe progressive form of RP, with symptoms of night blindness that occur during the first decade of life and progress to legal blindness by the third to fourth decade in most affected males (Flaxel et al., 1999). In this disease, high myopia is often observed from childhood in addition to retinal degeneration and electrophysiological abnormalities (Flaxel et al., 1999; Koenekoop et al., 2003). Mutations in *RPGR* (MIM #312610) account for the majority of X-linked RP, and these patients show high myopia in addition to RP (Sanchez Tocino et al., 2019). Similarly, mutations in *ARR3* (e.g. (van Mazijk et al., 2022; Xiao et al., 2016) and *OPN1LW*, mainly expressed in cone-photoreceptors, were also associated with high myopia (reviewed by (Neitz



and Neitz, 2021). Other syndromic and non-syndromic eye disorders associated with high myopia include Marfan syndrome (MIM #154700) (Pyeritz and McKusick, 1979), with mutations in *FBN1* (MIM #134797), Knobloch (MIM #267750) (summarized by (Aldahmesh et al., 2011), with mutations in *COL18A1* (MIM #120328), Wagner (MIM #143200), with mutations in *VCAN* (MIM #118661), Stickler syndrome (MIM #108300), with mutations in *COL2A1* (MIM #120140), Ehlers-Danlos syndrome (MIM#130000), with mutations in *COL5A1* (MIM# 120215) and Donnai-Barrow syndrome (MIM #222448) (Ohlsson, 1963), with mutations in *LRP2* (MIM #600073) (Kantarci et al., 2007). Based on these findings, it appears that disruption of the retinal signaling pathway from photoreceptors to the inner retina can lead to myopia. Interestingly, **common genetic variants** within or nearby genes that are associated with **syndromic myopia** are enriched for variants that **cause non-syndromic, common myopia** (Flitcroft et al., 2018). For most of the implicated genes, expression in the retina is documented. Reinforcing these findings, degeneration of photoreceptors and/or amacrine cells (ACs) in chicken retinas, has been associated with increased axial growth of the eye, leading to myopia (Ehrlich et al., 1990; Fischer et al., 1999). E.g. this was shown using colchicine to destroy amacrine cells, which normally suppress axial growth of the eye (Fischer et al., 1999).

Studies in chicken and mice showed that light dependent ON-bipolar cell (BC) dopamine signaling is a major player in the development and protection of myopia (Boatright et al., 1994; Boelen et al., 1998; Dumitrescu et al., 2009; Iuvone et al., 1978; Schaeffel and Feldkaemper, 2015; Stone et al., 2011). Retinal dopamine content is decreased in the absence of light and during myopia development (Schaeffel and Feldkaemper, 2015). It was shown, that intravitreal or topical application of levodopa, which is widely used in the treatment of neurological disorders involving dysregulation of the dopaminergic system, inhibits the

development of experimental myopia in chickens (Thomson et al., 2019). In addition, it has been demonstrated that non-myopic children treated for attention deficit hyperactivity disorder (ADHD) with dopaminergic agents have slower developmental myopic refraction than untreated peers, providing a more direct suggestion that dopamine plays a role in human refractive development (Gurlevik et al., 2021).

Patients with **complete congenital stationary night blindness (cCSNB)**, which represents a complete ON-BC dysfunction, with unaltered OFF-BC function present as well with high myopia (median error of -7.4 D) (Bijveld et al., 2013; Zeitz et al., 2015). Multiple mutations in cCSNB-associated genes such as *NYX*, *GRM6*, *GPR179*, *TRPM1* and *LRIT3* lead to this condition in patients and mouse models (Audo et al., 2012; Bech-Hansen et al., 2000; Dryja et al., 2005; Gregg et al., 2003; Koike et al., 2010; Li et al., 2009; Maddox et al., 2008; Masu et al., 1995; Morgans et al., 2009; Neuville et al., 2014; Orhan et al., 2021; Orlandi et al., 2012; Pardue and Peachey, 2014; Peachey et al., 2012; Pusch et al., 2000; Qian et al., 2015; van Genderen et al., 2009; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2015; Zeitz et al., 2005). cCSNB mouse models lacking *Nyx* (*nob*) and *Grm6* with ON-BC dysfunction, showed **increased susceptibility to myopia and decreased dopamine content** (Chakraborty et al., 2015; Pardue et al., 2008). While human subjects with cCSNB and high myopia have no **ON-BC transmission**, their OFF-BC transmission is largely intact (Miyake et al., 1986; Zeitz et al., 2015). By contrast, subjects with incomplete CSNB (iCSNB) show variable degrees of myopia (median refractive error of -4.8 D), associated with both reduced ON-and OFF-pathway dysfunction (Bijveld et al., 2013; Miyake et al., 1986; Zeitz et al., 2015). We are not aware that high myopia has been reported with other forms of CSNB, leading to a rod dysfunction and a Riggs-ERG (Zeitz et al., 2015). Aleman et al showed that stimulation of the ON-pathway may thicken the choroid and thus perhaps inhibit myopia in humans (Aleman et

al., 2018). Together, these findings suggest that **ON-pathway disruption** contributes to the development of myopia and that studies on cCSNB can be used to better understand myopia.

In recent years, gene identification studies in CSNB patients led to the identification of key proteins mediating photoreceptor to ON-BC signal transmission. Because of the prevalence of myopia in CSNB patients, these ON-pathway genes are also candidate genes for myopia. Seeking new myopia genes through this purely genetic approach has its limitations since CSNB is a rare retinal condition (Zeitz et al., 2015); for example our data suggest that the prevalence of CSNB in France is ~1:400,000 (Varin, 2020), though it is likely to be under-diagnosed since correct diagnosis requires the application of a specific clinical examination (e.g. electroretinography) and/or molecular genetic testing. Given these limitations, we followed an alternative approach using whole transcriptome sequencing to seek novel CSNB-associated or CSNB-myopia related genes. This allowed us to **add novel proteins** to the retinal signaling pathway, identify new candidate genes for myopia, and **strengthen the evidence for several previously proposed myopia-associated** genes. These results provide a framework for the development of future therapeutic strategies to treat myopia.

## **2. Phenotype in human cases and animal models with complete congenital stationary night blindness (cCSNB) and associated myopia**

### **2.1. Signal transmission from photoreceptors to ON-bipolar cells**

The clinical characterization of subjects with CSNB, and more specifically **cCSNB**, was recently reviewed (Zeitz et al., 2015). **Electroretinography** is crucial for a correct positive diagnosis of CSNB and distinguish its different forms, both in human subjects and animal models (Zeitz et al., 2015). A clear diagnostic electroretinogram (ERG) feature in cCSNB is

the absence of the b-wave in dark adapted conditions (DA 0.01) (Figure 1). In light-adapted conditions (LA 3.0 30 Hz and LA 3.0), ERGs are altered differently (see for details (Zeitz et al., 2015)) (Figure 1). ERG findings under scotopic conditions highlight similarities between cCSNB animal models and the human phenotype. In contrast, under photopic conditions, cCSNB animal models show more variability between species (Figure 1). The photopic ERG phenotype of cCSNB mouse models is generally more severe, including the absence of the b-wave, compared to that of human cases or larger animal models (Figure 1) (e.g. (Neuille et al., 2014; Orhan et al., 2021)). In contrast, cone-driven responses are comparable between CSNB dogs, horses and human cases, i.e. mildly reduced and delayed (reviewed in (Kondo et al., 2015; Varin et al., 2021b; Witzel et al., 1978; Zeitz et al., 2015) (Figure 1). These differences may be a result of species-specific physiological differences, but could also be due to the use of different ERG protocols (Varin et al., 2021b).

ERG features associated with myopia in human subjects and animal models are less well studied (Koh et al., 2014; Westall et al., 2001).. Some studies in myopic chicken suggested that the oscillatory potentials are altered (Fujikado et al., 1997). By performing multifocal ERG measurements Ho et al., showed that ERG responses originating from the human paracentral retina negative defocus are reduced compared to ERG responses originating from the central retina (Ho et al., 2012). This paracentral region of the retina is believed to predominately reflect the activity from ON- and OFF-BCs, with relatively small contributions from photoreceptors and other inner retina cells (Chu et al., 2008). Because genetic data are often unavailable for myopia subjects, it remains uncertain if myopia cases that present specific ERG-alterations represent syndromic myopia cases, as found e.g. in cCSNB. For those genes that have been implicated in myopia, they may also have roles in ON-pathway signaling. For example, a mouse model of myopia lacking *Aplp2*, coding for the amyloid beta precursor like protein 2, which is highly expressed in bipolar cells, revealed a reduction in the

amplitude of the ERG b-wave and oscillatory potentials (Tkatchenko et al., 2015). A genome-wide-association study (GWAS) revealed an association between *APLP2* variants and myopia in humans; thus, the ERG defects in the *Aplp2*<sup>-/-</sup> mouse were thought to be linked to myopia (Tkatchenko et al., 2015) (Figure 2). However, the electrophysiological properties of the retina of the *Aplp2*<sup>-/-</sup> mouse model are also consistent with a role of APLP2 in synaptic transmission. It would be interesting to document ERGs of myopia cases linked to *APLP2*.

## **2.2. Visual acuity in cCSNB and myopia**

Subjects with cCSNB have decreased visual acuity with a median of 0.30 log MAR (Minimum Angle of Resolution; about 20/40) (Zeitz et al., 2015). Relatively preserved mean best corrected visual acuity of 0.02 log MAR (about 20/20; (Ye et al., 2019)) and 0.88 decimals (better than 20/25; (Liu et al., 2010)) is observed in myopic (including high myopic) subjects without underlying retinal changes. Pathologic myopia, however, is associated with a reduced mean best corrected visual acuity of  $0.56 \pm 0.35$  decimals (about 20/35; (Liu et al., 2010)) and  $0.19 \pm 0.20$  log MAR (about 20/30; (Ye et al., 2019)). About 30% of cases with myopic retinal changes have visual acuity worse than 20/60. Hence, although cCSNB subjects demonstrate high axial myopia (Al-Hujaili et al., 2019) their visual acuity loss is generally more severe, due to cone ON-bipolar cell dysfunction, than in subjects with isolated myopia.

Visual acuity in mice can be measured using an optomotor test (Jellali et al., 2005). All tested mouse models for cCSNB reveal severely reduced visual acuity under scotopic conditions (Neuille et al., 2014; Orhan et al., 2021; Pinto et al., 2007). Visual acuity under photopic conditions may be also altered (Neuille et al., 2014; Pinto et al., 2007; Varin et al., 2021b). A few studies have measured visual acuity in myopia mouse models; For example, in *Aplp2*

knock-outs visual acuity was normal in form-deprivation myopia, but contrast vision was reduced and correlated with myopia (Tkatchenko et al., 2015). Similarly, patients with myopia exhibited reduced sensitivity to contrast in comparison to emmetropes and contrast sensitivity decreased with an increasing degree of myopia (Stoimenova, 2007).

### **2.3. Retinal structure in cCSNB and myopia**

In contrast to progressive rod-cone dystrophy, the retinal structure is quite well preserved in human subjects with cCSNB. This is due to the stationary, functional, but not degenerative nature of disease of cCSNB. A few reports describe thinning of inner retinal layers (INLs) in cases with cCSNB as measured by spectral domain Optical Coherence Tomography (SD-OCT). However, this thinning is different from that observed in subjects with progressive rod-cone dystrophy (Al Oreany et al., 2016; Godara et al., 2012; Ivanova et al., 2019). SD-OCT measurements done in the *Lrit3* mouse model of cCSNB also revealed thinning of the INL (Neuille et al., 2014). It is not clear if the INL thinning observed in human cCSNB subjects and in a few mouse models is related to the development of high myopia or if it is only caused by the mutated gene causing cCSNB. A systematic analysis of cCSNB cases compared to myopia control cohorts is needed to determine the exact cause of this thinning (Zeitz et al., 2015).

In subjects with myopia without outer retinal changes, regional changes in central retinal thickness have been described by SD-OCT; these include thinning of the INL and outer nuclear layer, and thickening of OPL and photoreceptor outer segments (Liu et al., 2015; Ye et al., 2019). In subjects with pathologic myopia, additional changes described under the term of myopic maculopathy are observed (Ohno-Matsui et al., 2016).

### 3. Studying myopia in mouse models

Animal models have been increasingly used to investigate mechanisms of myopia. Myopia can be induced using negative lenses or form deprivation in a variety of species as diverse as monkeys (Qiao-Grider et al., 2007; Weinstein and Grether, 1940), tree shrews (Norton and McBrien, 1992; Petry et al., 1984), cats (Berkley and Watkins, 1973; Blake et al., 1974), guinea pigs (Buttery et al., 1991; Howlett and McFadden, 2007), chickens (Irving et al., 1996; Jarvis et al., 2009; Schmid and Wildsoet, 1998), and fish (Shen and Sivak, 2007). However, most these models are not well suited for genetic research.

The mouse, has become a popular animal model for the myopia research (Barathi et al., 2014; Barathi et al., 2013; Beleggia et al., 2015; Cases et al., 2015; Hudson et al., 2015; Ma et al., 2014; Miyake et al., 2015; Pardue et al., 2008; Song et al., 2016; Storm et al., 2014; Tekin et al., 2013; Tkatchenko et al., 2012; Tkatchenko et al., 2015; Tran-Viet et al., 2013; Wu et al., 2015a; Wu et al., 2015b). The mouse offers a number of important advantages compared to other species, including well-established techniques allowing the alteration of its genome. Moreover, both genes and environment can be manipulated in the same mouse (Barathi et al., 2008; Schaeffel et al., 2004; Tejedor and de la Villa, 2003a; Tkatchenko et al., 2010). Behavioral studies suggest that vision is critical for accurate spatial navigation in mice (Buhot et al., 2001; Cook et al., 2001; de la Cera et al., 2006; Faulstich et al., 2004). Although mice are classified as nocturnal animals they are also active during the day and have diurnal retinal features (Flores et al., 2007; Jacobs, 2013; Yang et al., 2009). Mice undergo emmetropization driven by photopic visual stimulation similar to humans (Tkatchenko et al., 2013). Basic spatial and temporal vision characteristics in mice are similar to those in humans (Histed et al., 2012; Umino et al., 2008) but with lower visual function compared to humans (Prusky and Douglas, 2004). Due to the above-mentioned differences, thresholds for rod-dominated

(scotopic) and cone-dominated (photopic) vision in mice, as well as the structure of the retinal scotopic and photopic pathways, maybe different but still show high similarities to those in humans (Leamey et al., 2008; Umino et al., 2008). Although mice lack the *fovea* found in primates, the mouse retina has an area of increased density of photoreceptors and retinal ganglion cells (RGC) just temporal to the optic disc, which represents an anatomical and functional analog of the *area centralis* found in all non-primate mammals (Drager and Olsen, 1981; Jeon et al., 1998; Leamey et al., 2008). Induced changes in genetic background and gene-targeted mutations affect refractive eye development and susceptibility to myopia in mice (Schipper et al., 2007; Tkatchenko et al., 2015; Tkatchenko et al., 2019; Troilo et al., 2019; Wisard et al., 2011; Zhou et al., 2001; Zhou et al., 2010). Experimental myopia can be induced in mice using visual **form deprivation (form deprivation myopia, FDM)** or **negative spectacle lenses (lens-induced myopia, LIM)**, similar to other animal models (Chakraborty et al., 2014a; Pardue et al., 2008; Pardue et al., 2013; Park et al., 2013; Schaeffel et al., 2004; Tejedor and de la Villa, 2003b; Tkatchenko et al., 2015) (Figure 3).

Susceptibility to FDM was increased in mouse models with a defect in the ON-pathway (Chakraborty et al., 2015; Pardue et al., 2008), highlighting that ON-pathway disruption may be an important element in refractive error development. More specifically, **cCSNB-associated myopia** as shown by myopic shifts in eyes with FDM was observed in mice lacking *Nyx* (nob) (Gregg et al., 2003) and *Grm6* (Masu et al., 1995) (Chakraborty et al., 2015; Pardue et al., 2008). We hypothesize that the cCSNB models used in the present study will similarly show a greater susceptibility to FDM- or LIM-induced myopia, although the genetic background of the mice must be considered, as this can strongly influence both the baseline and susceptibility to induced myopia. For example, wild-type mice in a “129 background” show high baseline myopia (~ -20D) compared to those in a C57BL/6J background (Tkatchenko et al., 2019). Our cCSNB models lacking *Gpr179* and *Lrit3* are in a



C57BL/6J background; in contrast, our cCSNB mouse model lacking *Grm6* is in a different genetic background (129S6.129S(Cg)) than the one used by Chakraborty et al., 2015 (Chakraborty et al., 2015). Thus, we estimate that the difference of the refractive error following FDM or LIM may not be measurable in our mice lacking *Grm6*. Recently we were indeed able to show that our cCSNB model lacking *Gpr179* is more susceptible to LIM (Wilmet et al., 2022 under review).

All cCSNB mouse models share the same gene defects as human subjects with cCSNB (Audo et al., 2012; Bech-Hansen et al., 2000; Dryja et al., 2005; Gregg et al., 2003; Pardue et al., 1998; Peachey et al., 2012; Pusch et al., 2000; Zeitz et al., 2013; Zeitz et al., 2015; Zeitz et al., 2005). All cCNSB genetic defects result in a defective ON-BC transmission. In contrast, disruption of mainly the OFF-pathway caused by a mutation in the *Vsx1* gene did not significantly alter refractive eye development or the susceptibility to experimentally induced FDM (Chakraborty et al., 2014b). These findings lend further support to the selective contribution of the ON-pathway to myopia at least in animal models. Recently it was shown that *Vsx1* is expressed in both cone ON- and OFF-BCs, but not in rod ON-BCs (Shekhar et al., 2016). We are not aware of studies showing myopia in mice with iCSNB, which affects both ON- and OFF-BCs. However, in a recent study, patients with a variant near *GJD2* had high myopia, supporting a potential role for altered signaling in cone-driven OFF pathways in myopia development. Therefore, it is possible that multiple retinal pathways contribute to myopia (Jiang et al., 2022).

Numerous retinal signaling pathways have been shown to be involved in refractive eye development and myopia in animal models (Summers et al., 2021; Tkatchenko and Tkatchenko, 2019; Troilo et al., 2019). Dopamine signaling plays an important role in these

processes and **dopamine (DA) and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC)** have been implicated in refractive error development in mice (Schaeffel and Feldkaemper, 2015). Stimulation of DA biosynthesis in light is due to the activation of tyrosine hydroxylase (TH) (Iuvone et al., 1978). Dopaminergic ACs receive excitatory glutamatergic input from ON-BCs (Boatright et al., 1994; Boelen et al., 1998; Dumitrescu et al., 2009; Stone et al., 2011) and transmit the signal further to RGCs in the retina. Retinal DA and DOPAC content drop during the development of FDM and remain at reduced levels (Schaeffel and Feldkaemper, 2015). Further support for the role of DA in myopia development comes from the cCSNB mouse models lacking *Nyx (nob)* and *Grm6*, as they are characterized by not only an **increased susceptibility to FDM but also by lower levels of DA and DOPAC (*nob* mice) and DOPAC (*Grm6*<sup>-/-</sup>) compared to wild-type animals** (Chakraborty et al., 2015; Pardue et al., 2008). Compared to measuring the refractive error in animal models with FDM or LIM, measuring DA and DOPAC by ultra-performance liquid chromatography is less time consuming, since the induction of experimental myopia is not needed. Indeed, recent findings revealed that levels of DOPAC are reduced in genetic retinal disease mouse models and are not affected by myopia induction (Chakraborty et al., 2015; Park et al., 2013). As shown in Figure 4, we detected lower levels of DA and DOPAC after light adaptation in mice lacking *Gpr179*, *Lrit3* and *Grm6* compared to wild-type animals, further demonstrating that these cCSNB mouse models provide a valid basis to study myopia.

## **4. Differentially expressed genes in cCSNB**

### **4.1. RNA-Seq studies in mouse models for cCSNB**

Several studies have identified novel myopia-associated candidate genes by whole transcriptome sequencing in several animal models of myopia (Riddell and Crewther, 2017;

456 Riddell et al., 2016; Tkatchenko et al., 2019; Tkatchenko and Tkatchenko, 2021a, b;  
457 Tkatchenko et al., 2018; Vocale et al., 2021; Wu et al., 2018). Here, we performed whole  
458 transcriptome sequencing (RNA-Seq) in three different adult mouse models of cCSNB  
459 (*Gpr179*<sup>-/-</sup>, *Lrit3*<sup>-/-</sup> and *Grm6*<sup>-/-</sup>) and their age-matched littermates (each, n = 5) to investigate  
460 the molecular basis of myopia in cCSNB and to identify novel proteins involved in the retinal  
461 signaling cascade, including the ON-pathway. After identification and validation of  
462 differentially expressed genes (DEGs), a meta-analysis was performed by comparing our data  
463 with i) published transcriptomic data from purified retinal cells and single cell RNA-Seq data  
464 (Macosko et al., 2015; Shekhar et al., 2016; Siegert et al., 2012; Siegert et al., 2009; Woods et  
465 al., 2018) and ii) pathway analyses and myopia databases and/or publications concerning the  
466 role of identified DEGs in normal vision. Figure 5 shows DEGs with fold changes (FC) of at  
467 least 1.2, P-values of  $\leq 0.01$  and an expression value of at least 5 transcripts per million reads  
468 (TPM) from RNA-Seq data of adult *Gpr179*<sup>-/-</sup>, *Lrit3*<sup>-/-</sup> and *Grm6*<sup>-/-</sup> mice compared to data  
469 from age-matched wild-type littermates (Supplementary Table S1-S4). As expected, all three  
470 mouse models exhibited significantly lower expression of their respective “knocked out”  
471 genes (*Gpr179*, *Lrit3*, *Grm6*) compared to the corresponding wild-type strains  
472 (Supplementary Tables S1-S4). Overall, 155, 133, and 222 genes were differentially  
473 expressed in the *Gpr179*<sup>-/-</sup>, *Lrit3*<sup>-/-</sup> and *Grm6*<sup>-/-</sup> mouse strains, respectively (Supplementary  
474 Tables S1-S4 and Figure 5a). Differences in numbers and types of DEGs between the strains  
475 may be due in part to differences in genetic background, which may also influence differential  
476 regulation of the gene network (Tkatchenko et al., 2019). While cCSNB mouse models  
477 lacking *Gpr179* and *Lrit3* are on a C57BL/6J background, mice lacking *Grm6* are on a  
478 129S6.129S(Cg) background. However, to minimize background related issues, for each  
479 knock-out strain, the respective littermate wild-type strain was used for comparison. DEGs,  
480 appearing in all three cCSNB mouse strains may be implicated in a common physiological

role, while DEGs appearing in only one cCSNB mouse strain may have a unique role important for the specific gene missing in the model. Here, we focused mainly on DEGs shared by at least two of the three mutant strains.

## 4.2. Validation of RNA-Seq studies

To identify genes playing a role in the cCSNB phenotype, DEGs with at least 1.2 FCs and P-value  $\leq 0.01$  were investigated, including their expression in specific retinal cell-types and their association with the term “myopia”. Overall, there were 52 DEGs, that appeared in at least two cCSNB mouse strains (Supplementary Table S5 and S6) and 7 in all three (Supplementary Table S6, bold, Figure 5A and B). The *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mouse strains shared the majority of the DEGs (38), followed by *Gpr179*<sup>-/-</sup> and *Grm6*<sup>-/-</sup> (16) and *Grm6*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mouse strains (12) (Figure 5A). The 52 DEGs present in at least two mouse strains could be sorted into 10 clusters (Figure 5B). The largest cluster consisted of genes down-regulated in the cCSNB models (cluster 1, Figure 5B). Quantitative RT-PCR (RT-qPCR) performed for 24 of those genes confirmed that all 24 were differentially expressed in the retina of knock-out mouse strains compared to the corresponding wild-type mice (Figure 6 shows some of the validated genes, Supplementary data). Of note, some genes were found to be differentially expressed only in mice lacking either *Lrit3* or *Gpr179* genes by RNA-Seq, but were found to be significantly differentially expressed in all three knock-outs by RT-qPCR (e.g. *Prkca* and *Tpbp*, Figure 6). Although not all differences observed with RNA-Seq were validated by RT-qPCR, which may be explained by the lesser sensitivity of RT-qPCR experiments (Costa et al., 2013), the trend was the same for the majority of the 24 DEGs, thus validating the transcriptome sequencing approach.

## 4.3. Known genes implicated in CSNB

Mutations in *NYX*, *GRM6*, *GPR179*, *TRPM1* and *LRIT3* that cause cCSNB affect protein localization in retinal ON-BCs (Audo et al., 2012; Bech-Hansen et al., 2000; Dryja et al., 2005; Li et al., 2009; Peachey et al., 2012; Pusch et al., 2000; van Genderen et al., 2009; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2005). The proteins localize in the outer plexiform layer (OPL) and in most cases in the dendritic tips of ON-BCs (Zeitz et al., 2015). Similar to human subjects, ON-BC function is affected in cCSNB mouse models (Gregg et al., 2003; Koike et al., 2010; Masu et al., 1995; Morgans et al., 2009; Neuville et al., 2014; Peachey et al., 2012; Zeitz et al., 2015). Proteins involved in cCSNB often show an interdependency in their localization, and may or may not show correlated changes in expression levels (Neuville et al., 2015). For example, nyctalopin (encoded by *Nyx*) and TRPM1 interact. Localization of TRPM1 at the ON-BC dendritic tips is dependent on the presence of nyctalopin, mGluR6 and LRIT3 (Cao et al., 2011; Hasan et al., 2020; Neuville et al., 2015; Pearing et al., 2011; Zeitz et al., 2015). Using RNA-Seq, we showed that *Trpm1* mRNA levels are dependent on the expression of *Gpr179*, *Lrit3*, and *Grm6*, and that expression levels of *Grm6* are dependent on the expression of *Lrit3* (Figure 7). However, although *Trpm1* expression levels seems to be dependent on *Gpr179* expression, the localization of TRPM1 at the dendritic tips of BCs does not appear to be affected in *Gpr179*<sup>-/-</sup> mice (Orhan et al., 2021; Orlandi et al., 2012). Aside from the targeted gene in each knock-out strain, most of the other known genes underlying cCSNB, are not strongly differentially expressed (Supplementary Tables S1 and S6), suggesting that the 52 DEGs in the cCSNB mouse models are not necessarily candidate genes for cCSNB.

#### 4.4. Transcriptome analyses of DEGs in cCSNB

529 All 52 DEGs that we identified are expressed in the human retina (Supplementary Table S6,  
 530 Figure 8) (Farkas et al., 2013). Most of them were already reported in retina transcriptome  
 531 databases (Blond and Leveillard, 2019; Farkas et al., 2013; Kalathur et al., 2008; Macosko et  
 532 al., 2015; Shekhar et al., 2016; Siegert et al., 2012; Siegert et al., 2009). Here, we mainly  
 533 focus either on genes expressed in ON-BCs or in downstream ACs and RGCs. Twenty genes  
 534 (*5730419F03Rik*, *Cxcr7*, *Ampd3*, *Arc*, *Bdnf*, *Cacna1s*, *Car8*, *Lect1*, *Edn2*, *Eomes*, *Gabrr1*,  
 535 *Ldb2*, *Lrp2bp*, *Olfm3*, *Plekhf1*, *Rgs16*, *Slco5a1*, *Syn2*, *Tgfb2* and *Tpbg*) showed an age-  
 536 dependent relative increase in expression in the *rd1*-transcriptome database, as a result of the  
 537 age-dependent photoreceptor degeneration (Blond and Leveillard, 2019; Kalathur et al.,  
 538 2008). These genes are expressed in the INL or ganglion cell layer (GCL) and they seem to be  
 539 important for BC, AC and RGC function and maintenance (Supplementary Table S6). In  
 540 addition, a number of novel candidate genes absent in the current transcriptome databases  
 541 were also identified. Several of these genes were found in rod (*Col5a1* and *Vgll4*), cone  
 542 (*Cxcr7*, *Car8*, *Casp7*, *Gabrr1*, *Ptprr*, *Spred3*, *Tac2* and *Tpbg*), rod-cone (*Lect1*, *Gng4*, *Tgfb2*  
 543 and *Trpc1*), BC (*Cxcr7*, *Bdnf*, *Cacna1s*, *Car8*, *Casp7*, *Ccnjl*, *Cdc25c*, *Lect1*, *Col5a1*, *Dusp4*,  
 544 *Gabrr1*, *Gng4*, *Grm6*, *Ldb2*, *Lrp2bp*, *Plekhf1*, *Prkca*, *Ptprr*, *Rgs16*, *Slco5a1*, *Spred3*,  
 545 *St6galnac5*, *Tac2*, *Tpbg*, *Tgfb2*), AC (*Arc*, *Cxcr7*, *Car8*, *Lect1*, *Fbxo32*, *Gabrr1*, *Gng4*,  
 546 *Ldb2*, *Olfm3*, *Plekhf1*, *Ptprr*, *Tac2*, *Tgfb2*, *Tpbg* and *Vgll4*) and RGC (*Cxcr7*, *Car8*, *Lect1*,  
 547 *Eomes*, *Gabrr1*, *Gng4*, *Plekhf1*, *Ptprr*, *Tgfb2*, *Trpc1*, *Tpbg* and *Vgll4*) databases (Figure 8).  
 548 Interestingly, *5730419F03Rik*, *Ampd3*, *Car8*, *Casp7*, *Ccnjl*, *Lect1*, *Dusp4*, *Gabrr1*,  
 549 *Gm20754*, *Lrp2bp*, *Prkca*, *Ptprr*, *Rgs16*, *Slco5a1* and *Tpbg* were also shown to be  
 550 differentially expressed in mice lacking the BC-specific basic helix-loop-helix (bHLH)  
 551 transcription factor, Bhlhe23, *alias* Bhlhb4 (Bramblett et al., 2004; Woods et al., 2018). This  
 552 transcription factor was found to be expressed in rod bipolar cells (RB). ERGs in the adult  
 553 *Bhlhb4* knockout mice, in a C57Bl6 strain, showed that the loss of BHLBH4 resulted in

disrupted rod signaling and profound retinal dysfunction resembling CSNB, characterized by the loss of the scotopic ERG b-wave. A depletion of INL cells in the adult *Bhlhb4* knockout has been ascribed to the abolishment of the RB cell population during postnatal development. Other retinal cell populations including photoreceptors were unaltered. In the absence of information from these databases, our data was completed using expression data available from the literature and single cell RNA-Seq analyses (<https://www.proteinatlas.org>) (Supplementary Table S6, Figure 8).

Strikingly, *Lect1* (*Cnmd*) was up-regulated in *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mice and slightly down-regulated in *Grm6*<sup>-/-</sup> mice compared to wild-type mice. These findings were validated by RT-qPCR (Figure 5B, cluster 2, Figure 6). In contrast, *Etv4* was down-regulated in *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mice and up-regulated in *Grm6*<sup>-/-</sup> mice compared to wild-type animals (Figure 5B, cluster 9).

**LECT1** (MIM# 605147), coding for the leukocyte cell-derived chemotaxin 1 protein (also called chondromodulin 1) is an angiogenesis inhibitor first isolated from fetal bovine cartilage. Although confined to cartilage and the eye at later stages of development, fetal whole-mount *in situ* hybridization revealed expression of *Lect1* mRNA in somites, heart, bronchial arches, roof plate, **retina** and limb buds. *LECT1* expression pattern suggested a role in morphogenesis during embryonic development (Shukunami et al., 1999). In adult retina, LECT1 was found in the GCL and INL as revealed by RNA *in situ* hybridization and immunohistochemistry studies (Funaki et al., 2001). A knock-out mouse model showed no overt abnormality during embryogenesis (Brandau et al., 2002; Nakamichi et al., 2003). Analysis of expression databases revealed that *LECT1* is expressed in the inner retina,

photoreceptors, BCs, ACs and RGCs and that its expression appears to be reduced in *Bhlhe23*<sup>-/-</sup> mice (Woods et al., 2018).

#### 4.4.1. Single cell analyses of DEGs in subpopulation of bipolar cells

To investigate in which BCs (rod BCs, cone ON- or OFF-BCs) the more abundant DEGs were expressed, our data was compared to a single-cell BC-specific transcriptome database (Shekhar et al., 2016). We found that most genes were enriched in rod BCs and cone ON-BCs, but some were also expressed in OFF-BCs (BC1-4 = OFF-BCs, BC5-BC7 = ON-BCs (Figure 9). These data are further explored below for genes where additional functional information has been described previously.

#### 4.5. Pathway analyses of DEGs involved in CSNB and correlation with myopia

In rare cases, subjects with mutations in *NYX* (Yip et al., 2013; Zhang et al., 2007; Zhou et al., 2015), *TRPM1* (Zhou et al., 2016) and *GRM6* (Jin et al., 2017; Xu et al., 2009) present with early-onset high myopia despite the absence of documented cCSNB diagnosis. However, it is believed that most mutations in *NYX*, *LRIT3*, *TRPM1*, *GRM6* and *GPR179* are not directly responsible for high myopia. Instead, it is hypothesized that myopia in cCSNB is caused by a disruption of the ON-pathway (Chakraborty et al., 2015). Our analysis revealed that **mitogen-activated protein kinase (MAPK) pathways, synaptic signaling, G protein-coupled receptor ligand binding pathways, and proteins implicated in eye, endoderm and connective tissue development** were affected in cCSNB (Figure 10A). Some of the genes appeared in multiple pathways (Figure 10B). In the following paragraphs we detail these genes and pathways and describe correlations between cCSNB and associated ocular alterations, focusing on myopia. When genes appeared in multiple pathways, they are described only once. In addition, we focus on genes with additional data available in the literature. These genes are highlighted in bold. A detailed description of all DEGs, their



expression pattern in different cell types of the retina, their roles and putative involvement in myopia development can be found in the supplementary data and supplementary Tables S6 and S7).

#### 4.5.1. MAPK pathway

To our knowledge, the MAPK signaling pathway has not previously been implicated in cCSNB. In the normal retina, phosphorylated MAPKs are barely detectable. However, subjects and mice lacking functional retinoschisin (RS1) exhibit decreased ERG b-wave amplitudes and increased MAPK activation (Gehrig et al., 2007; Plossl et al., 2017). In addition, under certain pathological conditions, such as induced retinal ischemia, MAPKs are activated by phosphorylation in several retinal layers, including in the INL with a concomitant reduction of the b-wave amplitude (Zeitz et al., 2015). Interestingly, **inhibitors of MAPK phosphorylation** significantly normalized the b-wave amplitude after ischemia (Roth et al., 2003). Although MAPK signaling in the retina has been investigated, its role in cCSNB and accompanying ocular manifestations are poorly understood. Fifteen DEGs associated with the MAPK pathway were identified: *Ackr3/Cxcr7*, *Bdnf*, *Cacna1s*, *Casp7*, *Ccnjl*, *Cdc25c*, *Dusp4*, *Ldb2*, *Prkca*, *Ptprr*, *Spred3*, *Synj2*, *Tgfb2*, *Tpbp* and *Vgll4* (Figures 10 and 11).

**LRIT3** (MIM# 615004) encoding leucine-rich repeat, immunoglobulin-like, and transmembrane domain-containing protein 3 (LRIT3) is mutated in human subjects with cCSNB (MIM# 615058) and mice (Neuille et al., 2014). Interestingly, LRIT3 is itself a modulator of the fibroblast **growth factor receptor 1** (FGFR1) (Kim et al., 2012), which also plays an important role in the MAPK signaling pathway, though not identified as such in pathway analyses. Phosphorylated FGFR1 regulates different signaling pathways including **MAPK**.

626

627 **TGFB2** (MIM# 190220) encodes the transforming **growth factor** beta 2 (Supplementary  
628 Table S6 and S7, Figures 8-11). Mice lacking *Tgfb2* exhibit perinatal mortality and a wide  
629 range of developmental defects, including congenital heart defects, skeletal defects and **eye**  
630 defects (Sanford et al., 1997), which suggests that TGFB2 also plays a role in eye  
631 development, albeit with a different outcome dependent on the species tested. Studies in tree  
632 shrews revealed that expression of *Tgfb2* was reduced in animals with experimentally  
633 **induced myopia** (Jobling et al., 2004) but increased in the experimentally-induced myopia  
634 guinea pig model (Chen et al., 2013). Studies of **human aqueous humor** also found that  
635 levels of TGFB2 positively correlated with axial length in cases with **myopia** (Jia et al.,  
636 2014). In addition, a genetic variant in *TGFB2* (Lin et al., 2009) and the myopia Harmonize  
637 GAD database (Rouillard et al., 2016) linked *TGFB2* to myopia (Supplementary Tables S6  
638 and S7). To our knowledge, a connection between down-regulation of *TGFB2* in inner retinal  
639 cells, including rod BCs and cone ON-BCs, and myopia has not been previously established.

640

641 **BDNF** (MIM# 113505) encoding brain-derived neurotrophic factor (B)DNF (Supplementary  
642 Table S6 and S7, Figures 8-11) serves as a survival, mitogenic, and differentiation factor in  
643 both the developing and adult central and peripheral nervous systems (reviewed in (Klockner et  
644 al., 2000)). The cellular effects of neurotrophins are mediated by the activation of Trk tyrosine  
645 kinase receptors and the p75 receptor. Upon binding to these receptors, neurotrophins are  
646 known **to activate** various intracellular signal transduction pathways, including the MAPK  
647 pathway (Figure 11), which affect cell survival and cell death mechanisms. BDNF is  
648 expressed in the inner retina (Herzog and von Bartheld, 1998) including all bipolar cells  
649 (Supplementary Table S6, Figures 8 and 9). Its neuroprotective and healing properties in these

cells are well known (Afarid et al., 2016). Several polymorphisms in *BDNF* have been associated with myopia (Musolf et al., 2017). In addition, *BDNF* appeared in the myopia Harmonize GAD database (Rouillard et al., 2016) (Supplementary Table S6 and S7, Figure 8).

***ACKR3*** (MIM# 610376), also known as ***CXCR7***, and located on chromosome **2q37.3**, encodes the atypical chemokine receptor 3. It is expressed in several regions of the CNS, in endothelial and various immune cells (Salazar et al., 2014), as well as in retina (Supplementary Table S6, Figures 8-11). *ACKR3* is able to heterodimerize with *CXCR4*, which increases ligand stimulated membrane recruitment of  $\beta$ -arrestin, thus **causing sustained activation** of the ERK1/2 and p38 MAPK signaling pathways (Quinn et al., 2018) (Figure 11). Interestingly, *ACKR3/ CXCR7* was linked to **myopia** in a mapped region on chromosome **2q37** (Figure 8) (Schache et al., 2009). A few mutations in *ACKR3* have been shown to cause **oculomotor synkinesis**, characterized by involuntary eye movements in mouse and humans (Whitman et al., 2019).

***CACNA1S*** (MIM# 114208), coding for the L-type voltage-dependent calcium channel,  $\alpha$ -1S subunit, is required for normal skeletal and cardiac muscle function (Elbaz et al., 1995)). *CACNA1S* is homologous to other calcium channel  $\alpha$ -1 subunits, such as *CACNA1F* (Cav1.4), which is mutated in subjects with incomplete CSNB (Bech-Hansen et al., 1998; Strom et al., 1998). In the retina, *Cacna1s* was found to be expressed in BCs and more recently in cones and rods (Supplementary Table S6, Figures 8-11). Initially, it was thought to localize in dendritic tips of ON-BCs, similar to other genes implicated in cCSNB (Specht et al., 2009; Tummala et al., 2014) but its exact protein localization in the retina remains

unclear, since commercially available CACNA1S antibodies have been shown to cross-react with GPR179 (Hasan et al., 2016), which is localized at the dendritic tips of ON-BCs. Calcium channels and their subunits in general have been linked to MAPK signaling (Ikeda, 2001) (Figure 11). L-type voltage-gated calcium channels in both retinal photoreceptors and bipolar neurons are under **circadian control** (Hull et al., 2006; Ko et al., 2009; Ko et al., 2007).

**PRKCA** (MIM# 176960) encodes protein kinase C, alpha (PKCalpha, PRKCA), which is a calcium-activated, phospholipid- and diacylglycerol (DAG)-dependent **serine/threonine-protein kinase** (Supplementary Table S6, Figures 8-11). It is involved in regulation of cell proliferation, apoptosis, differentiation, migration and adhesion, tumorigenesis, cardiac hypertrophy, angiogenesis, platelet function and inflammation, by directly phosphorylating targets or activating signaling cascades involving ERK1/2 (Figure 11). In the retina, PRKCA present at glutamatergic rod-BC synapses could act as a molecular switch to trigger intracellular signaling cascades in response to the activation of G-protein-coupled receptors (Woods et al., 2018). Its role in activating MAPK pathways or in cCSNB have not been studied. We found reduced expression of *Prkca* in cCSNB models by RNA-Seq and validated it by RT-qPCR (Figure 6). In addition, we showed a trend for reduced PRKCA protein levels in *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mice (Figure 12). PRKCA expression at both transcript and protein levels in *Grm6*<sup>-/-</sup> mice was more variable (compare Figure 6 and Figures 12). A reduced PRKCA immunofluorescent labeling was also seen in *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mice (Figure 13).

**PTPRR** (MIM: 602853) encoding protein-tyrosine phosphatase receptor type R, (PTPRR) was found to be expressed in many different retinal cells including in rod BCs and cone ON-

BCs (Supplementary Table S6 and S7, Figures 8-11). PTPRR has been implicated in MAPK **deactivation** in the brain (for review (Chirivi et al., 2007)). Mice lacking *Ptprr* showed increased phosphorylation of ERK1/2 in Purkinje cells and impaired motor coordination (Chirivi et al., 2007). In the retina, PTPRR was suggested to play an important role in neuronal development and maintenance of the mature retina (Horvat-Brocker et al., 2008). Mutations in *PTPRR* could be involved in the development of **myopia** by a change in the enzyme's ability to bind to, or dephosphorylate MAPK, leading to increased MAPK growth signals. Increased expression of *PTPRR* in rapidly growing fetal retina and choroid may be the result of normal developmental or growth regulation, suggesting that PTPRR plays a role in controlling **ocular growth**. Disruption of this protein's function may account for the rapid eye growth seen in highly myopic individuals during early childhood, which slows in adulthood. As growth decreases, the need for this protein would be reduced (Hawthorne et al., 2013). In addition, *PTPRR* was identified by **GWAS as linked to myopia** (Supplementary Table S6 and S7).

**TPBG** (MIM# 190920), encoding trophoblast glycoprotein (Supplementary Table S6 and S7, Figures 8-11), was found **to activate** MAPK signaling in smooth muscle cells and adventitial pericyte-like cells (Spencer et al., 2019). TPBG is directly connected to ACKR3 (**CXCR7**; see above). Indeed, TPBG silencing downregulated phosphorylated ERK and ACKR3. In the retina, TPBG is highly expressed by rod-BCs, where it has been shown to exhibit PRKCA-dependent phosphorylation (Wakeham et al., 2020; Wakeham et al., 2019). TPBG phosphorylation was decreased in *Prkca*<sup>-/-</sup> compared to wild-type mice. Our studies revealed lower expression of *Tpbg* at the mRNA level, and a trend of lower protein levels in all cCSNB mouse strains (Figures 7 and 12). In addition, TPBG immunofluorescence was severely

reduced in the OPL and inner part of the IPL representing the dendritic tips and synaptic terminals of rod-BCs, in mice lacking *Lrit3* and *Gpr179* (Figure 13).

**VGLL4** (MIM# 6186962) encodes vestigial-like family member 4 (Supplementary Table S6 and Figures 8-11). Studies in zebrafish (Xue et al., 2018), xenopus (Barrionuevo et al., 2014; Faucheux et al., 2010) and mice suggested that VGLL4 takes part in early embryonic development, including eye development. Interestingly, this gene is a part of the Hippo signaling pathway, which has also been implicated in myopia (Zhu et al., 2018).

**DUSP4** (MIM# 602747 alias *MKP-2*), located on chromosome 8p12, codes for dual-specificity phosphatase 4 (Guan and Butch, 1995). It belongs to the DUSP protein family **that inactivates** their target kinases, namely MAPKs, by dephosphorylating both phosphoserine/threonine and phosphotyrosine residues. Expression of DUSP proteins is induced by various extracellular stimuli, and has diverse tissue distribution and subcellular localization (Dickinson and Keyse, 2006; Patterson et al., 2009). In melanocytes, *DUSP4* expression may be regulated by the microphthalmia-associated transcription factor (MITF), which is a melanocytic lineage-specific transcription factor with a role in the development of malignant melanoma. Similarly, MITF regulates *TRPM1* expression, which is implicated in both cCSNB and melanoma-associated retinopathy (MAR) (Hoek et al., 2008; Li et al., 2009; van Genderen et al., 2009; Varin et al., 2020; Xiong et al., 2013). Targeting the MAPK signaling pathway has transformed the treatment of metastatic melanoma. It has been recently shown that the genetic inactivation of DUSP4 reduced the proliferation of melanoma cells, thus making DUSP4 an interesting therapeutic target (Christodoulou et al., 2021). *DUSP4* is expressed in different tissues, including the eye, and more importantly in retinal BCs

(Supplementary Table S6, Figures 8-11). In tissues other than the retina, *DUSP4* was mainly localized to the **nucleus** and found to be **induced** by multiple agents, including serum, growth factors, UV-light, and oxidative stress. Depending on the tissue, it **dephosphorylates** MAPKs, such as ERK, JNK or p38 (Figure 11). In addition, DUSP4 was shown to play a role in innate and adaptive immunity, in cancer, and in brain function (Lawan et al., 2012; Seternes et al., 2019). Supporting our RNA-Seq findings, a significant downregulation of *Dusp4* expression was found in *Lrit3*<sup>-/-</sup> and *Gpr179*<sup>-/-</sup> mice by RT-qPCR and a trend was noted in *Grm6*<sup>-/-</sup> mice (Supplementary Figure 1). In *Trpm1*<sup>-/-</sup> mice, significantly reduced expression of *Dusp4* was also observed (Supplementary Figure 1). These findings were confirmed at the protein level, but with more variability (Figure 12). Western blot analyses of retinal extracts from wild-type mice revealed a band at 43 kDa, the calculated molecular weight of DUSP4. This band was absent in *Dusp4*<sup>-/-</sup> mice (data not shown). The role of DUSP4 in the retina is largely unknown. Transcriptional profiling of endogenous germ layer precursor cells identified *Dusp4* as an essential gene in zebrafish endoderm specification (Brown et al., 2008). Although most of the vertebrate eye is derived from the ectoderm (Bassnett and Sikic, 2017), zebrafish *Dusp4* morphants had small necrotic heads, suggesting an essential role of DUSP4 in anterior development (Brown et al., 2008). However, the role of DUSP4 in eye development was not further described. Interestingly, in well-established models of refractive error induction, *Dusp4* appeared to be down-regulated in the eye upon inductions of both FDM and LIM in chicks and mice (McGlenn et al., 2007; Stone et al., 2011; Tkatchenko et al., 2016). Subjects with an 8p deletion, which includes the 8p12 *DUSP4*, often present with eye defects including nystagmus, strabismus and myopia, among other clinical syndromes (<https://www.rarechromo.org/media/information/Chromosome%20%208/8p%20interstitial%20deletions%20including%208p12%20FTNP.pdf>) (e.g. (Beighle et al., 1977; Chilcote et al., 1987; Devriendt et al., 1999; Klopocki et al., 2006)). Such defects are also found in cCSNB

cases. Together, these findings suggest that *DUPS4* may be one of the genes that underlies cCSNB-related **high myopia** (Supplementary Table S6, Figure 8).

#### 4.5.2. Synapse

Several signaling pathways involved in synaptic transmission were strongly associated with cCSNB (Figure 10A), including glutamatergic, serotonergic, cholinergic and GABAergic (gamma-aminobutyric acid) signaling. GABA is one of the major inhibitory neurotransmitters of the retina and central nervous system (Cheng et al., 2011). Twelve DEGs were associated with GABAergic signaling: *Ackr3/Cxcr7*, *Cacna1s*, ***Car8***, ***Edn2***, ***Gabrr1***, *Gng4*, ***Grm6***, *Prkca*, *Ptprr*, ***Rgs16***, *Tac2* and *Trpc1* (Figure 10A). A detailed description of their expression in the different cell types of the retina, focusing on the inner retina, as well as their function and possible involvement in myopia can be found in the supplementary data (Supplementary Tables S6 and S7) and Figure 8).

***GABRR1*** (MIM# 137161), coding for the gamma-aminobutyric acid receptor, rho-1 (GABRR1) (alternatively named GABA-C Receptor, rho-1 subunit), is a member of a family of ligand-gated chloride channels that are the major inhibitory neurotransmitter receptors in the central nervous system (Cutting et al., 1991). It represents one of the subunits of the GABA-C receptor (rho1-rho3) (e.g. (Enz, 2001)) expressed in the inner retina in cone photoreceptors, bipolar cells and horizontal cells (Supplementary Table S6, Figures 8 and 9). In addition, GABRR1 was found to be differentially expressed in bipolar cell-deficient *Bhlhe23*<sup>-/-</sup> mice (Woods et al., 2018). Mice deficient for the *Gabrr1* subunit lacked GABA-C receptor-mediated GABA-evoked responses, and signaling from rod BCs to third order cells was altered (McCall et al., 2002). The elimination of GABRR1 was demonstrated to result in



795 the absence of GABA-C receptors in the retina. While global retinal morphology was not  
796 affected and the scotopic electroretinogram revealed a normal shape of the a-wave (rod-  
797 function) and b-wave (mainly rod-BC function), the implicit time of the b-wave was shorter  
798 and more oscillatory potentials (OPs) were found in mice lacking *Gabrr1* (McCall et al.,  
799 2002). It has been suggested that some of the OPs are generated by a negative feedback loop  
800 in the IPL between the GABAergic ACs and the axon terminals of rod BCs (Kolb and Nelson,  
801 1981), which may indicate that the altered ERG is due to a transmission defect between ACs  
802 and rod BCs. Together, these findings confirm that GABRR1 has an important function in  
803 normal visual processing. Several studies identified an association between *GABRR1* and  
804 myopia (Supplementary Table S6 and Figure 8). A genome-wide association study identified  
805 *GABRR1* as one of the genes associated with refractive error in Asian populations (Fan et al.,  
806 2016; Lin et al., 2020). TPMPA ((1,2,5,6-tetrahydropyridin-4-yl)methylphosphinic acid)), a  
807 GABA-C antagonist has been shown to inhibit synaptic transmission in rat spinal cord (Rozzo  
808 et al., 1999), modulate sleep-waking behavior in rats (Arnaud et al., 2001), enhance memory  
809 in chicks (Gibbs and Johnston, 2005) and most importantly, inhibit **myopia** development in  
810 chicks and guinea pigs (Chebib et al., 2009; Cheng et al., 2014; Stone et al., 2003), indicating  
811 possible roles for GABA-C receptors in memory, **circadian rhythms**, and **myopia** (Cheng et  
812 al., 2011). Although GABA-C receptors are pentameric structures formed from three possible  
813 subunits, the rho1 subunit, encoded by *Gabrr1*, was found to be the primary target of GABA-  
814 C antagonists (cis- and trans-(3-aminocyclopentanyl)butylphosphinic acid (cis- and trans-3-  
815 ACPBPA) inhibiting myopia (Chebib et al., 2009). In addition to its expression in the retina,  
816 *Gabrr1* is also expressed in the fibrous and cartilaginous layers of the chick sclera, where it is  
817 localized to the sclera fibroblasts and chondrocytes, which have been previously connected to  
818 myopia (Cheng et al., 2011). Together, these findings are consistent with reduced levels of

*Gabrr1* expression in cCSNB (Figure 6), as a possible cause for the development of high myopia in cCSNB.

**CA8** (MIM# 114815) and its mouse orthologue *Car8*, encoding carbonic anhydrase VIII (CA8), has been found to be important for GABAergic synaptic transmission. *Car8* is mainly expressed in the inner retina, with some expression in cone photoreceptors (Supplementary Table S6, Figures 8 and 9). In addition, it was found to be differentially expressed in *Bhlhe23*<sup>-/-</sup> mice (Woods et al., 2018). *Car8* has been mostly studied in the brain, where it is highly expressed in cerebellar Purkinje neurons (Jiao et al., 2005; Kato, 1990) and other parts of the brain (Lakkis et al., 1997). Mice lacking functional *Car8* (Jiao et al., 2005) show gait ataxia and dystonia with some ultrastructural differences in synapses between Purkinje cell dendritic spines, indicating a role for carbonic anhydrase VIII in synapse formation and/or maintenance. Similarly, subjects with mutations in *CA8* exhibit ataxia and mild mental retardation (Turkmen et al., 2009). Recent studies in mouse retina showed CAR8 immunolabelling in rod BCs co-labelled for PRKCA, with particular bright staining in the axon terminal regions and weaker staining in the cytoplasmic compartments (Puthussery et al., 2011). In addition, some labelling was observed in a subset of cone BCs and GABAergic ACs (Puthussery et al., 2011). Mice lacking *Car8* do not have a CSNB phenotype, as measured by electroretinography, but light-evoked current responses from AII-ACs were significantly larger and more prolonged than in control mice, suggesting that CAR8 is important for modulating retinal neurotransmission (Puthussery et al., 2011). Interestingly, genome-wide association studies found a potential association between *CA8* and myopia (Kiefer et al., 2013) (Supplementary Table S6 and Figure 8). The reduced expression of *Car8* in *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mice, as identified by RNA-Seq studies, was confirmed by RT-qPCR and at the protein level (Figures 6 and 12).

844

845 **GRM6** (MIM# 604096) encodes metabotropic glutamate receptor 6 (GRM6 or mGluR6),  
846 which has been well described as causing cCSNB when mutated (Dryja et al., 2005; Zeitz et  
847 al., 2005) and which we used here as a mouse model (Masu et al., 1995) to identify DEGs in  
848 cCSNB. *Grm6* seems to be the only “cCSNB gene” with a significantly reduced expression in  
849 other cCSNB models (here *Lrit3*<sup>-/-</sup>), indicating that the expression of *Lrit3* may influence  
850 *Grm6* transcript levels. *Grm6* is uniquely expressed in ON-BCs, where the ON-visual  
851 pathway originates (Supplementary Table S6) (Zeitz et al., 2015). As mentioned above,  
852 several studies have described mutations in *GRM6* (Jin et al., 2017; Xu et al., 2009) that have  
853 been associated with early-onset high myopia despite undocumented cCSNB (Supplementary  
854 Table S7, Figure 8).

855

856 **RGS16** (MIM# 602514) encodes regulator of G-protein signaling 16, which is expressed in  
857 the inner retina (Dhingra et al., 2008) (Supplementary Table S6 and Figures 8 and 9) and  
858 differentially expressed in *Bhlhe23*<sup>-/-</sup> mice (Woods et al., 2018). While other regulatory  
859 proteins such as GNB5 (GTP-binding protein beta 5), RGS9 and RGS11 are known to be  
860 implicated in ON-BC signal transduction, the role of RGS16 in this signaling cascade remains  
861 to be elucidated. Further, we are not aware of a link between *RGS16* and retinal disorders,  
862 including myopia. Genome-wide association studies revealed a variant in this gene associated  
863 with **circadian rhythms** in individuals claiming to be morning persons (Hu et al., 2016).  
864 Interestingly, *Rgs16*<sup>-/-</sup> mice were shown to have a longer circadian period (Doi et al., 2011).

865

866 **EDN2** (MIM# 131241) encodes endothelin2 (EDN2). *Edn2* is one the few genes expressed at  
867 higher levels in cCSNB mouse strains compared to the wild-type mice (Supplementary Table

S6, Figures 5 and 10A). It was found to be a potent vasoconstrictor that binds to two G protein-coupled receptors, i.e., EDNRA (which resides on bipolar dendrites) and EDNRB (which is present on Mueller and horizontal cells). Both receptors are also present on choroidal vessels (Prasanna et al., 2003). Interestingly, it has been shown that *Edn2* was also up-regulated in the retina of several models of photoreceptor degeneration (Chen et al., 2004; Cottet et al., 2006; Rattner and Nathans, 2005; Van Schil et al., 2016), as well as following retinal damage, such as retinal detachment (Rattner and Nathans, 2005; Zacks et al., 2006). These observations suggest that increased expression of *Edn2* may be a general response to retinal insult (reviewed in (Bramall et al., 2013)). *EDN2* was linked to myopia by a recent genome-wide association study (Tedja et al., 2018), suggesting its increased expression as a potential cause of cCSNB-related myopia (Supplementary Table S6 and Figure 8).

***LRP2BP*** (MIM# 619020) encodes low density lipoprotein receptor-related protein 2b (LRP2B). We are including it here among BC synaptic proteins because of its apparent retinal localization (Woods et al., 2018) (Supplementary Table S6 and Figure 8). LRP2BP is a scaffold protein, known to bind and recruit proteins to the megalin receptor (LRP2), which participates in endocytosis and signal transduction (Petersen et al., 2003). Interestingly, mutations in *LRP2* cause the Donnai-Barrow/Facio-Oculo-Acoustico-Renal syndrome, which is partially characterized by high-grade myopia (Kantarci et al., 2007; Stora et al., 2009). Histological investigations of ocular mouse tissues also identified a severe myopia phenotype in megalin-deficient mice (Storm et al., 2014) and suggested that LRP2 is required for normal eye growth (Cases et al., 2015). Similarly, a zebrafish model for *Lrp2* developed myopia (Veth et al., 2011). Even more importantly, *LRP2BP* is located on chromosome 4q35.1, a region deleted in cases with high myopia, among other disorders (Manolakos et al., 2013; Rossi et al., 2009) (Figure 8).

893

894 *SLCO5A1* (MIM# 613543) encoding solute carrier organic anion transport family, member  
895 5A1 (SLCO5A1), was also included in this section, because of a recent finding suggesting  
896 that this protein is an important component of retinal synapses and appears to be localized in  
897 the OPL (Woods et al., 2018). It is not clear if it is also located elsewhere in the retina  
898 (Supplementary Tables S6 and Figure 8). Subjects with the mesomelia-synostoses syndrome  
899 have many extraocular disorders but may also present with myopia. This syndrome is due to a  
900 non-recurrent microdeletion on chromosome 8q13 encompassing *SULF1* and *SLCO5A1*  
901 (Isidor et al., 2010) (Figure 8).

902

#### 903 **4.5.3. GPCR ligand binding**

904 Signaling related to **G protein-coupled receptor ligand binding** was also overrepresented in  
905 our database. Twelve different genes were associated with G protein-coupled receptor ligand  
906 binding, i.e., *Ackr3/Cxcr7*, *Bdnf*, *Edn2*, *Gng4*, *Grm6*, *Plekhf1*, *Prkca*, *Tac2*, *Tgfb2*, *Tpbp*,  
907 *Trpc1* and *Umodl1* (Figure 10). A description of their expression patterns in different cell  
908 types of the retina, focusing on the inner retina, and their putative role in myopia can be found  
909 in the supplementary data (Supplementary Tables S6 and S7 and Figure 8).

910

911 One of these genes, *UMODL1* (MIM# 613859) encodes an extracellular matrix adhesion and  
912 cellular migration uromodulin-like 1 protein (UMODL1) (Di Schiavi et al., 2005; Shibuya et  
913 al., 2004). It is known to be expressed in olfactory and vomeronasal sensory neurons (Di  
914 Schiavi et al., 2005). It is also present in retina gene expression databases, but the specific cell  
915 types expressing *Umodl1* remain unknown. *UMODL1* was found to be associated with

myopia in a genome-wide association study (Nishizaki et al., 2009) (Supplementary Tables S6, S7 and Figure 8).

#### 4.5.4 Eye, endoderm, and connective tissue development

The vertebrate eye is a complex organ. Its development is guided by highly organized processes that take place during embryonic development, and mutations in key genes involved in these processes lead to severe congenital disorders as well as myopia (Graw, 2010). Several DEGs identified in cCSNB mouse models were associated with **eye, endoderm and connective tissue development**, including *Arc*, *Bdnf*, *Cacna1s*, *Cnmd/Lect1*, *Col5a1*, *Eomes*, *Etv4*, *Dusp4*, *Grm6*, ***Olfm3***, *Prkca*, *Spred3*, *Tgfb2*, *Unmodl1* and *Vgll4* (Supplementary Tables S6 and S7, Figures 7 and Figure 10).

**ARC** (MIM# 612461) encodes the activity-regulated cytoskeleton-associated protein (ARC) (Supplementary Table S6 and Figure 8). ARC mRNA is rapidly produced and delivered into dendrites following synaptic activity in neurons (Dynes and Steward, 2007). Interestingly, its expression in rodent brains is robustly induced by prolonged **wakefulness** (Cirelli and Tononi, 2000). Converging evidence has led to the hypothesis that wakefulness potentiates, and sleep reduces, **synaptic strength**. Recently, ARC was demonstrated to be important for the induction of multiple behavioral and molecular responses associated with sleep homeostasis (Suzuki et al., 2020).

**COL5A1** (MIM# 120215) encodes the type V collagen alpha-1 (COL5A1) protein, which belongs to group V and XI collagens. These collagens control fibrillogenesis, probably by

forming a core within the fibrils. Another characteristic of these collagens is the partial retention of their N-propeptide extensions (Fichard et al., 1995). Collagen V was found to be expressed in the human placenta and skin, but later studies showed that it is also present in other organs. Our transcriptome meta-analyses revealed that *Col5a1* is expressed in rods and in BCs in the retina (Supplementary Table S6 and Figure 8). Mutations in *COL5A1* were found in subjects with the classic type 1 Ehlers-Danlos syndrome (MIM#130000). Ehlers-Danlos syndromes (EDS) are a group of heritable connective tissue disorders that share the common features of skin hyperextensibility, articular hypermobility, and tissue fragility. The main features of classic Ehlers-Danlos syndrome are loose-jointedness and fragile, bruisable skin that heals with peculiar 'cigarette-paper' scars (Beighton, 1970). Ophthalmic clinical features have also been described, including retinal detachment (Pemberton et al., 1966) and high pathologic myopia (Gharbiya et al., 2012; Perez-Roustit et al., 2019).

***EOMES*** (MIM# 604615) encodes eomesodermin (*EOMES*), also called *Tbr2*. It is directly regulated by *Brn3b* and is important for RGC development (Mao et al., 2008). In agreement with these observations, our gene expression data revealed that *Eomes* is mainly expressed in the inner retina and more specifically, in RGCs (Supplementary Table S6 and Figure 8). Homozygous silencing of *EOMES* leads to microcephaly with polymicrogyria and corpus callosum agenesis (Baala et al., 2007). We are not aware of a retinal phenotype in subjects with this gene defect; however, mice lacking *Eomes* (alias *Trpb2*) have reduced retinal projections to non-image-forming brain nuclei and an attenuated pupillary light reflex (Sweeney et al., 2014). Interestingly, subjects with CSNB have a reduced redilation and smaller baseline pupil diameters, suggesting a disinhibition of intrinsically photosensitive RGCs due to affected post-photoreceptor transduction via BCs (Schatz et al., 2019).

963

964 ***OLFM3*** (MIM# 607567), encoding olfactomedin 3, is a downstream target of PAX6, which  
965 plays a critical role in eye development (Grinchuk et al., 2005). Although the function of  
966 *OLFM3* is not yet understood, it may be involved in cell-cell adhesion and cell attachment to  
967 the extracellular matrix, and affect cell migration and axon growth (Grinchuk et al., 2005).  
968 Our gene expression data revealed that *Olfm3* is expressed in ACs in the retina  
969 (Supplementary Table S6 and Figure 9). *OLFM3* was also implicated in glaucoma and  
970 myopia (Supplementary Table S6 and Figure 8) (Podkolodnaya et al., 2011).

971

#### 972 **4.5.5. Genes not associated with any pathway, unknown function and limited amount of** 973 **expression in the retina**

974 Several not confirmed but annotated mouse genes (*5730419F03Rik*, *Dbhos* (dopamine beta  
975 hydroxylase, opposite strand, long coding RNA), *Gm20754*, *Gm40477*, *Gm49760* and  
976 *Gm5478*) of unknown function and only limited information about their retinal expression  
977 patterns were differentially expressed in several cCSNB mouse lines (Supplementary Table  
978 S6). Two genes (*5730419F03Rik* and *Gm20754*) appeared to be also differentially expressed  
979 in mice lacking *Bhlhe23*. In addition, *5730419F03Rik* is most likely expressed in the inner  
980 retina, suggesting that it may have a role in inner retinal signaling. Interestingly, *Dbhos* was  
981 also differentially expressed in mice exposed to blue light (Ouyang et al., 2020). Future  
982 studies aimed at investigating the exact cellular expression patterns of these genes and their  
983 roles in the retina, as well as identification of the human orthologs will shed light on their  
984 contribution to retinal pathophysiology.

985 Although some information is available about the expression in the retina of the following  
986 DEGs, *AFAP1L1* (MIMI# 614410), *Pdzph1*, *PLEKHF1* (MIM# 615200), *ST6GALNAC5*



(MIMI# 610134) and *MAST2* (MIM# 612257) (Supplementary Table S6, supporting material), their roles in retinal physiology and possible pathologies remains to be elucidated.

#### **4.5.6 Other genes from myopia databases that are differentially regulated in at least one mouse model with cCSNB**

Several other genes identified in myopia databases appear to be significantly differentially expressed as determined by RNA-Seq analyses in at least one mouse model of cCSNB (Supplementary Tables S6 and S7 and Figure 8).

### **5. Cause of reduced expression of many DEGs in cCSNB**

Reduced expression of DEGs and their respective proteins in cCSNB may be due to reduced expression levels or a lower number of cells expressing the DEGs. Genes implicated in cCSNB share a common phenotype, namely an ON-BC signaling defect. Although the morphology of the retina in human subjects and animal models with cCSNB is believed to be non-degenerative and stable, subtle cellular changes have been described in mice lacking *Lrit3* and *Trpm1* (Neuille et al., 2014; Takeuchi et al., 2018). SD-OCT revealed thinning of the INL, IPL, GCL, and nerve fiber layer in *Lrit3*<sup>-/-</sup> mice (Neuille et al., 2014). This was not found in *Gpr179*<sup>-/-</sup> mice (Orhan et al., 2021). Interestingly, rod BC terminals were significantly smaller in *Trpm1*<sup>-/-</sup> retinas than in *Grm6*<sup>-/-</sup> retinas, suggesting that deficiency of TRPM1, but not GRM6 affects rod BC synaptic terminal maturation and alter signaling between rod BCs and ACs (Kozuka et al., 2017).

Notably, we found that *Prkca* transcripts were reduced in cCSNB retinas, and that, similar to TPBG, the level of PRKCA protein, which is specifically localized to rod BCs, was greatly reduced in *Gpr179*<sup>-/-</sup> and *Lrit3*<sup>-/-</sup> mice, but not in *Grm6*<sup>-/-</sup> mice (Figure 13), while the numbers of nuclei present in the INL were unaffected (Figure 14). Visualizing synapses with a protein-independent marker needs to be performed to evaluate if the lower amounts of PRKCA and TPBG are due to morphological changes in rod BCs, particularly their synaptic terminals. Similarly, we found that levels of DA and DOPAC were also reduced in cCSNB retinas. Since the number of nuclei in the INL (Figure 14), remained unchanged in the cCSNB mouse models, and reduction of TH-positive dopaminergic amacrine cells was not significantly different in cCSNB compared to wild-type mice (tested for *Gpr179*<sup>-/-</sup> versus *Gpr179*<sup>+/+</sup>) (Figure 15), we conclude that the reduced expression of some genes in cCSNB, as well as the reduction in DA and DOPAC levels are not due to degeneration of retinal cells, but may be linked to altered synapse morphology and/or lower RNA expression and/or reduced protein levels. We speculate that the absence of cCSNB genes such as *Gpr179* and *Lrit3*, leads to the classical ERG-defect but that other differentially regulated genes may contribute to myopia in those subjects with cCSNB. Similarly, exposure to reduced light levels in genetically unaffected individuals may also lead to lower expression of these genes and thus to myopia.

## 6. Future perspectives

### 6.1. Identification of differentially expressed genes in cCSNB models using a whole transcriptomic approach may yield novel proteins important for retinal signaling, as well as novel myopia-related genes

Mutations in *NYX*, *GRM6*, *GPR179*, *TRPM1* and *LRIT3* likely lead to cCSNB because the encoded proteins are necessary for ON-BC signaling (Audo et al., 2012; Bech-Hansen et al.,

2000; Dryja et al., 2005; Li et al., 2009; Peachey et al., 2012; Pusch et al., 2000; van Genderen et al., 2009; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2005). The retina of cCSNB human subjects is generally well preserved and the disease course is non-progressive. The proteins are localized in the outer plexiform layer and, in most cases, in the dendritic tips of rod BCs and cone ON-BCs (Zeitz et al., 2015). Mouse models of cCSNB show a similar ON-BC transmission defect as human cases. The diagnosis is confirmed by an electronegative waveform at the full-field electroretinogram with severely reduced or absent b-wave under scotopic and photopic conditions, reflecting defective ON-pathway signaling (Zeitz et al., 2015). Candidate genes causing this disorder have been identified by linkage analyses in humans, using animal models, and more recently, by next-generation sequencing approaches (e.g.(Audo et al., 2012; Pusch et al., 2000; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2005)), with the help of transcriptomic data-bases to reinforce candidate genes (Zeitz et al., 2015). Recently, Woods et al. used comparative transcriptomic analyses in a mouse model lacking the rod BC transcription factor *Bhlhe23* (also known as BHLHB4 or basic helix-loop-helix family member, b4), to identify potential genes implicated in CSNB (Woods et al., 2018). The phenotype of *Bhlhe23*<sup>-/-</sup> mice is slightly different than that of cCSNB. Although both phenotypes are stationary, rod BCs are almost completely absent in mice lacking *Bhlhe23*, resulting in a thinner INL but the cone pathway is not affected; thus *Bhlhe23*<sup>-/-</sup> mice have an isolated rod BC defect, while both, rod BC and cone ON-BC functions are affected in cCSNB. This is also reflected by the b-wave amplitude only being affected under scotopic, but not photopic conditions in *Bhlhe23*<sup>-/-</sup> mice (Bramblett et al., 2004). While the phenotype of *Bhlhe23*<sup>-/-</sup> mice is different from cCSNB, night vision may indeed be affected. To date, however subjects with mutations in *BHLHE23* and a similar phenotype have not been described (Woods et al., 2018). This might be due to the fact that only scotopic vision is affected, and ERG recordings are required to detect such a phenotype in affected subjects.

Because of the absence of rod BCs, one might expect that some of the genes differentially expressed in *Bhlhe23*<sup>-/-</sup> mice may be important for night vision. However, expression of only a few of the “cCSNB-genes” was significantly reduced in *Bhlhe23*<sup>-/-</sup> mice compared to wild-type mice. Furthermore, mice deficient for genes expressed at lower levels, such as mice lacking *Car8*, did not exhibit a typical cCSNB phenotype (Puthussery et al., 2011). This is consistent with our findings, indicating that while these approaches may identify novel candidates for cCSNB this is not necessarily the case.

It is important to note that cCSNB is characterized not only by night blindness, but also by high myopia, nystagmus and often strabismus. Strikingly, since cCSNB is present from birth and young subjects are often not aware of their vision defects in dim light conditions, they are often first diagnosed due to their high myopia and/or infantile nystagmus. Thus, a main goal of this work was to identify other genes implicated in the same pathway as proteins underlying cCSNB and in that way identify additional candidates for the other associated ocular abnormalities associated with cCSNB. Since myopia represents one of the most common eye diseases worldwide, with increasing numbers of affected persons expected in coming years, we focused our study on DEGs implicated in cCSNB and associated with myopia.

## **6.2. Retinal expression of DEGs, pathway analyses and correlation to eye phenotypes**

To understand in which retinal cell types the 52 DEGs are expressed, we queried several retina expression databases, including single cell transcriptome databases, as well as PubMed

(<https://pubmed.ncbi.nlm.nih.gov/>) and search tools such as “Google” (<https://www.google.com/>) (Macosko et al., 2015; Shekhar et al., 2016; Siegert et al., 2012; Siegert et al., 2009; Woods et al., 2018). These data showed that almost all 52 DEGs are expressed in the human retina, including in photoreceptors, BCs, ACs and RGCs, but for only a few of them was their retinal function described in the scientific literature (Supplementary Table S6 and Figure 8). Several DEGs, expressed in various retinal cell types were found to be associated with retinal disorders. For example, genes expressed in rods photoreceptors have been implicated in rod-cone dystrophies. Another example are genes expressed in ON-BCs, for which the encoded proteins are localized at the dendritic tips, which have been implicated in cCSNB (Zeitz et al., 2015). Variants in *FRMD7* (MIM # 300628), coding for Ferm domain-containing protein 7, which is expressed in ACs (Yonehara et al., 2016), are associated with idiopathic nystagmus in mice and human subjects (MIM #310700) (Tarpey et al., 2006). Thus, other genes expressed in ACs may also be linked to nystagmus. The contribution of genes expressed in **ACs** to **nystagmus** was further substantiated in a study with cCSNB humans and mice lacking functional nyctalopin (Winkelman et al., 2019). Thus, DEGs described herein and expressed in ACs may contribute to nystagmus observed in subjects with cCSNB (Figure 8). Recently, Bui Quoc and Milleret suggested that an abnormal routing of the **RGC** axons at the level of the optic chiasm might cause an imbalance between contra-lateral and ipsi-lateral projections and thus lead to **strabismus** (Bui Quoc and Milleret, 2014). This might occur due to an abnormal expression of genes controlling **RGCs** axonal projections, and which may be differentially expressed in cCSNB. Further experiments and database analyses will be needed to determine if DEGs expressed in ACs and RGCs (Figure 9) contribute to nystagmus and strabismus observed in human subjects with cCSNB. In addition, these genes may also represent candidate genes in cases of isolated nystagmus and strabismus.

1106 Our meta-analysis examined the expression of DEGs and their correlation with myopia using  
1107 published literature and database analyses. About 50% of the 52 DEGs expressed in the  
1108 retina, have been already linked to myopia (Figure 8), reinforcing our hypothesis that genes  
1109 differentially expressed in cCSNB may cause the myopia phenotype observed in cCSNB.  
1110 Indeed, GWAS studies showed that several genes expressed in various retinal cell types  
1111 contribute to the development of myopia (Verhoeven et al., 2013). Some of the genes  
1112 implicated in myopia are functionally involved in processes that facilitate communication  
1113 between cells in the retina or control the ability of photoreceptors to respond to light. Some  
1114 others are involved in pre-natal eye growth and development (Verhoeven et al., 2013). There  
1115 is some overlap between genes previously described as being involved in myopia and those  
1116 described here. We assume that some of the others may represent novel myopia-related genes  
1117 (Hysi et al., 2020; Tedja et al., 2018; Verhoeven et al., 2013). Interestingly, many DEGs  
1118 described here, when deleted or part of deleted chromosomal regions, lead to severe  
1119 phenotypes that often include myopia. Our hypothesis is that the expression levels of these  
1120 genes are associated with high myopia observed in cCSNB which makes cCSNB a more  
1121 complex disorder than previously recognized. In addition, DEGs may also produce the  
1122 cCSNB-associated ocular alterations nystagmus and strabismus. Our results combined with  
1123 GWAS findings highlight the light-dependent retina-to-sclera signaling cascade that can cause  
1124 myopia if disrupted and outline potential pathobiological molecular drivers (Tedja et al.,  
1125 2018). It is unlikely that signals from the retina control scleral growth directly. Instead, it is  
1126 suggested that retinal signals are relayed by the RPE, choroid and ciliary body, which in turn  
1127 release signaling molecules to directly affect scleral growth (Wallman and Winawer, 2004).  
1128 Our findings using cCSNB models suggest that due to an altered ON-pathway the expression  
1129 of several genes becomes insufficient, which may result in myopia. We hypothesize, that

exposure to insufficient light levels, as found in children with not enough outdoor activities similarly leads to alterations of the ON pathway and myopia.

Not surprisingly, the cCSNB DEGs included genes that are important for synapse formation and signaling. In addition, MAPK pathways and developmental genes were identified by our study, and to our knowledge, their association with cCSNB is novel. These same genes, however, are well known to be involved in the development of myopia (Li and Zhang, 2017), further reinforcing our predictions that genes differentially expressed in cCSNB are indeed good candidates for cCSNB-associated high myopia, as well as serving as candidates for non-syndromic myopia. Other DEGs identified here were not associated with specific myopia-related search terms or pathways, but, because of their expression in the retina and described physiological function, may be nevertheless be associated with myopia. Interestingly, a few DEGs have been implicated in circadian rhythms. Circadian clocks are cellular oscillators that generate daily rhythms even in the absence of external timing cues (Dunlap, 1999; Pittendrigh, 1993) and have also been associated with eye growth and refractive error development (Chakraborty et al., 2018).

### 6.3 Novel candidate genes important for vision

The following DEGs represent genes not previously associated with myopia and may represent novel candidate genes underlying high myopia in cCSNB or other retinal disorders: *Adgra3/Gpr125*, *Afap1l1*, *Ampd3*, *Arc*, ***Cacna1s***, *Ccnjl*, *Cdc25c*, *Dbhos*, *Eomes*, *Etv4*, *Fbox32*, *Frem3*, *Gm20754*, *Gm40477*, *Gm49760*, *Gm5478/Krt6c*, ***Gng4***, *Insyn2b*, *Ldb2*, *Mast2*, *Mir670hg*, *Myh7b*, *Olfm3*, *Pdzph1*, *Plekhf1*, ***Prkca***, ***Rgs16***, *Shroom4*, *Spred3*, *St6galnac5*, *Synj2*, *Tac2*, ***Tpbg***, ***Trpc1*** and *Umodl1*. More analyses are needed to validate their putative functional roles in vision. For a few of them, highlighted in bold, animal models

or more functional analyses are available and may thus represent the best candidates to be analyzed in the future.

#### **6.4 Treatment of cCSNB and myopia**

Although cCSNB is believed to be a relatively mild non-degenerative stationary retinal disease, this study shows that gene defects causing cCSNB impact the expression of other genes important for the correct development of the retina and eye. Treatment efficacy may also be impacted. Indeed, at least in mice, cCSNB treatment was more successful in immature retina, and only under scotopic conditions (Hasan et al., 2019; Scalabrino et al., 2015; Varin et al., 2021a; Varin et al., 2021b), suggesting that the development of the retinal structure, e.g., synapse formation, is irreversibly impaired in cCSNB. These subtle changes of the retina may only be visible with sensitive methods such as immunohistochemistry or electron microscopy. Such developmental defects may be regulated by the genes differentially expressed in cCSNB identified in this study. Replacing the missing gene implicated in cCSNB, such as *GRM6* or *LRIT3*, by an AAV-approach may restore the correct localization of the corresponding protein and its function, but it is not clear if this will also restore the normal expression of the cCSNB-associated DEGs. Defects in developmental processes, such as synapse formation, may lead to the observed failure to rescue photopic vision in adult mice. Furthermore, whether an AAV-based therapeutic approach can cure myopia remains unclear. Although refractive errors associated with myopia can be corrected using optical correction, myopic subjects may still develop a number of other vision-threatening complications such as myopic macular degeneration, retinal tears, retinal detachment and glaucoma (Hornbeak and Young, 2009). Therefore, identifying therapeutic approaches to prevent the development of myopia would be beneficial. Pharmacological treatments may become important means to



prevent and/or slow the progression of myopia, but they are unlikely to be able to revert or cure established myopia.

#### **6.4.1 Pharmacological myopia treatment**

A signaling cascade, which begins in the retina, via photoreceptors, BCs and dopaminergic, GABAergic, and glycinergic ACs, and propagate across all ocular tissues to the sclera is likely to contribute to human myopia development and progression (reviewed by (Tkatchenko and Tkatchenko, 2019)). This signaling cascade is triggered by optical blur, which plays a critical role in this process. Here, we suggest that cCSNB is an additional valuable model to study myopia, because the disruption of inner retinal signaling in cCSNB has a significant impact on refractive eye development, potentially similar to a low light environment. As discussed above, the neurotransmitter **DA and its metabolite DOPAC** have been proposed to regulate refractive eye development and their retinal concentrations are reduced in myopia models (Chakraborty et al., 2015; Pardue et al., 2008; Stone et al., 1989; Zhou et al., 2017). Here, we have shown that DA and DOPAC levels are also reduced in the retina of cCSNB mice. **Intravitreal injections** of **DA** in rabbits (Gao et al., 2006) and **intraperitoneal injections** of DA in guinea pigs (Mao et al., 2010) and mice (Landis et al., 2020) inhibit FDM myopia induction. Enhancing DA signaling by daily intraperitoneal injections of non-selective **DA receptor agonists** prevented FDM in chicken, guinea pig, monkey and mice (reviewed by (Zhou et al., 2017)). More studies are needed, however, to define the cellular mechanisms of DA action, a requirement for the development of an effective myopia treatment. **Bright light** has also been shown to protect against the development of myopia and to increase DA release in a number of studies with **animal models and in children** (reviewed by (Zhou et al., 2017)). It has been suggested that retinal DA **may induce choroidal thickening and inhibit ocular**

**growth** by triggering the release of other transmitters such as **nitric oxide (NO)** from the retina or choroid (reviewed by (Zhou et al., 2017). **Clinical trials** testing the use of **dopaminergic agents** to treat amblyopia, myopia and attention deficit disorders revealed **negative side effects of systemic activation of DA** signaling (reviewed by (Zhou et al., 2017)). In contrast, local delivery of DA by APO eye drops given to infant rhesus monkeys reduced development of FDM in the absence of systemic toxicity and other negative side effects (Iuvone et al., 1991). Despite these promising findings, we are not aware of further studies in non-human primates or clinical trials using dopaminergic compounds to inhibit myopia progression.

A few other pharmacological agents targeting neurotransmitter receptors have been shown to suppress the development of experimental myopia in animals, such as the **muscarinic acetylcholine receptor (mAChR) antagonists** pirenzepine and atropine, which are expected to act on muscarinic receptors, expressed in the sclera and in the inner retina. Further long-term clinical studies with large samples sizes are needed to validate the efficacy of this potential anti-myopia therapy (reviewed (Tkatchenko and Tkatchenko, 2019; Wang et al., 2021)). Today, however, **atropine**, a **nonselective muscarinic receptor antagonist**, is the most widely used anti-myopia drug, although the exact mechanism of atropine's inhibitory effect on myopia is not well understood. Several clinical trials using atropine eye drops in combination with optical devices such as multifocal lenses that impose a peripheral positive defocus, showed positive outcomes, albeit with low efficacy (reviewed (Tkatchenko and Tkatchenko, 2019)). It would be interesting to investigate if atropine, potentially together with optical devices would also inhibit myopia development in CSNB patients and animal models.

The recent identification of **signaling pathways**, identified by us here and others (Tkatchenko and Tkatchenko, 2019)), that control the response of the eye to optical defocus and susceptibility to myopia may be helpful for the development of new myopia therapies.

1227 Interestingly, many of those pathways play important roles in multiple retinal cell types and in  
1228 multiple ocular tissues. For example, the MAPK pathway and GABA receptor signaling  
1229 influence myopia development via multiple retinal cell types as well as the RPE/choroid  
1230 (reviewed (Tkatchenko and Tkatchenko, 2019)). Our study found that genes implicated in the  
1231 MAPK pathway are differentially regulated in cCSNB, suggesting they may contribute to  
1232 myopia in these subjects. Inhibitors of MAPK phosphorylation have been shown to inhibit  
1233 myopia (She et al., 2021), but we are not aware of clinical trials testing this target.

1234 Inhibition of GABA activity, such as with **GABA receptor antagonists, may prevent**  
1235 **excessive myopia** (reviewed (Wang et al., 2021)). Schmid et al. suggested that the  
1236 GABAergic pathway may interact with the dopaminergic pathway and that the balance  
1237 between excitatory and inhibitory signaling is important for normal eye growth (Schmid et al.,  
1238 2013). This is in line with our findings. Interestingly, we found that *Gabrr1*, coding for the  
1239 rho-1 GABA receptor subunit, and expressed in rod BC synaptic terminals (McCall et al.,  
1240 2002) is significantly downregulated in mice lacking *Gpr179* and *Lrit3*. It is possible that this  
1241 decrease in GABA receptors is a consequence of an increased release of GABA from  
1242 amacrine cells, leading in turn to myopia in cCSNB. Moreover, abnormal visual processing  
1243 was observed in mice lacking *Gabrr1* (McCall et al., 2002) and several studies linked the  
1244 human orthologue with myopia (Supplementary Table S6 and Figure 9) (Fan et al., 2016; Lin  
1245 et al., 2020). We are not aware of clinical trials testing GABA receptor antagonists for myopia  
1246 prevention, most likely because such drugs would be expected to have dangerous side effects.

1247 Further understanding of additional signaling pathways and ocular tissues implicated in  
1248 myopia and their interactions with various environmental factors will lead to the development  
1249 of anti-myopia therapies (Tkatchenko and Tkatchenko, 2019)). Considering the complexities  
1250 of the signaling cascades underlying myopia development, an ideal anti-myopia drug (or a  
1251 drug combination) would target multiple pathways. Although cCSNB appears to be a good

myopia model, refractive errors are only measured following experimental myopia inductions. Alternatively, treatment efficacy could be evaluated by measuring the restoration of neurotransmitter and other metabolite levels or by experimentally assessing the normalization of gene expression within the gene regulatory networks involved in myopia development. Together, we and others showed that myopia is a complex disorder influenced by many genetic and environmental factors. Future studies are needed to develop therapies targeting these signaling cascades and determine the efficacy of potential treatment approaches (Brennan et al., 2021).

## **Acknowledgements**

We are thankful to Manuel Simonutti, Julie Degardin, Quenol Cesar and Ruben Goulet for their support on animal phenotyping (Institut de la Vision platform) and to the platform of animal housing at the Institut de la Vision, to Marie-Laure Niepon and Anais Potey for their support on histological and quantification techniques (Institut de la Vision platform). We are grateful to Frank Schaeffel for fruitful discussions and advice concerning the myopia measurements in mice. The project was supported by Agence Nationale de la Recherche [ANR-12-BSVS1-0012-01\_GPR179], The Fondation pour la Recherche Medicale (FRM) in partnership with the Fondation Roland Bailly, Ile de Paris and Region Ile de France, LABEX LIFE- SENSES [reference ANR-10-LABX-65] supported by French state funds managed by the Agence Nationale de la Recherche within the Investissements d'Avenir programme [ANR-11-IDEX-0004-0], ]; IHU FOReSIGHT [ANR-18-IAHU-0001] supported by French state funds managed by the Agence Nationale de la Recherche within the Investissements d'Avenir

1276 program, Retina France, Association Française contre les Myopathies (AFM), Valentin Haüy,  
1277 Fondation Dalloz, UNADEV-Aviesan call 2015, Foundation Voir et Entendre, SENSGENE  
1278 and ERN-EYE and INSERM International Research Project (IRP 2021).

## References:

- Afarid, M., Torabi-Nami, M., Zare, B., 2016. Neuroprotective and restorative effects of the brain-derived neurotrophic factor in retinal diseases. *J. Neurol. Sci.* 363, 43-50.
- Al-Hujaili, H., Taskintuna, I., Neuhaus, C., Bergmann, C., Schatz, P., 2019. Long-term follow-up of retinal function and structure in TRPM1-associated complete congenital stationary night blindness. *Mol. Vis.* 25, 851-858.
- Al Oreany, A.A., Al Hadlaq, A., Schatz, P., 2016. Congenital stationary night blindness with hypoplastic discs, negative electroretinogram and thinning of the inner nuclear layer. *Graefes Arch Clin Exp Ophthalmol* 254, 1951-1956.
- Aldahmesh, M.A., Khan, A.O., Mohamed, J.Y., Alkuraya, H., Ahmed, H., Bobis, S., Al-Mesfer, S., Alkuraya, F.S., 2011. Identification of ADAMTS18 as a gene mutated in Knobloch syndrome. *J. Med. Genet.* 48, 597-601.
- Aleman, A.C., Wang, M., Schaeffel, F., 2018. Reading and Myopia: Contrast Polarity Matters. *Sci Rep* 8, 10840.
- Anera, R.G., Soler, M., de la Cruz Cardona, J., Salas, C., Ortiz, C., 2009. Prevalence of refractive errors in school-age children in Morocco. *Clin Exp Ophthalmol* 37, 191-196.
- Ang, M., Flanagan, J.L., Wong, C.W., Muller, A., Davis, A., Keys, D., Resnikoff, S., Jong, M., Wong, T.Y., Sankaridurg, P., 2020. Review: Myopia control strategies recommendations from the 2018 WHO/IAPB/BHVI Meeting on Myopia. *Br. J. Ophthalmol.* 104, 1482-1487.
- Arnaud, C., Gauthier, P., Gottesmann, C., 2001. Study of a GABAC receptor antagonist on sleep-waking behavior in rats. *Psychopharmacology (Berl.)* 154, 415-419.
- Audo, I., Bujakowska, K., Orhan, E., Poloschek, C.M., Defoort-Dhellemmes, S., Drumare, I., Kohl, S., Luu, T.D., Lecompte, O., Zrenner, E., Lancelot, M.E., Antonio, A., Germain, A., Michiels, C., Audier, C., Letexier, M., Saraiva, J.P., Leroy, B.P., Munier, F.L., Mohand-Said, S., Lorenz, B., Friedburg, C., Preising, M., Kellner, U., Renner, A.B., Moskova-Doumanova, V., Berger, W., Wissinger, B., Hamel, C.P., Schorderet, D.F., De Baere, E., Sharon, D., Banin, E., Jacobson, S.G., Bonneau, D., Zanolghi, X., Le Meur, G., Casteels, I., Koenekoop, R., Long, V.W., Meire, F., Prescott, K., de Ravel, T., Simmons, I., Nguyen, H., Dollfus, H., Poch, O., Leveillard, T., Nguyen-Ba-Charvet, K., Sahel, J.A., Bhattacharya, S.S., Zeitz, C., 2012. Whole-Exome Sequencing Identifies Mutations in GPR179 Leading to Autosomal-Recessive Complete Congenital Stationary Night Blindness. *Am. J. Hum. Genet.* 90, 321-330.
- Baala, L., Briault, S., Etchevers, H.C., Laumonnier, F., Natiq, A., Amiel, J., Boddaert, N., Picard, C., Sbiti, A., Asermouh, A., Attie-Bitach, T., Encha-Razavi, F., Munnich, A., Sefiani, A., Lyonnet, S., 2007. Homozygous silencing of T-box transcription factor EOMES leads to microcephaly with polymicrogyria and corpus callosum agenesis. *Nat. Genet.* 39, 454-456.
- Baird, P.N., Schache, M., Dirani, M., 2010. The GENes in Myopia (GEM) study in understanding the aetiology of refractive errors. *Prog. Retin. Eye Res.* 29, 520-542.
- Barathi, V.A., Boopathi, V.G., Yap, E.P., Beuerman, R.W., 2008. Two models of experimental myopia in the mouse. *Vision Res* 48, 904-916.

- 1 Barathi, V.A., Chaurasia, S.S., Poidinger, M., Koh, S.K., Tian, D., Ho, C., Iuvone, P.M.,  
2 Beuerman, R.W., Zhou, L., 2014. Involvement of GABA transporters in atropine-treated  
3 myopic retina as revealed by iTRAQ quantitative proteomics. *Journal of proteome research*  
4 13, 4647-4658.
- 5 Barathi, V.A., Kwan, J.L., Tan, Q.S., Weon, S.R., Seet, L.F., Goh, L.K., Vithana, E.N.,  
6 Beuerman, R.W., 2013. Muscarinic cholinergic receptor (M2) plays a crucial role in the  
7 development of myopia in mice. *Disease models & mechanisms* 6, 1146-1158.
- 8 Barrionuevo, M.G., Aybar, M.J., Tribulo, C., 2014. Two different vestigial like 4 genes are  
9 differentially expressed during *Xenopus laevis* development. *Int. J. Dev. Biol.* 58, 369-377.
- 10 Bassnett, S., Sikic, H., 2017. The lens growth process. *Prog. Retin. Eye Res.* 60, 181-200.
- 11 Bech-Hansen, N.T., Naylor, M.J., Maybaum, T.A., Pearce, W.G., Koop, B., Fishman, G.A.,  
12 Mets, M., Musarella, M.A., Boycott, K.M., 1998. Loss-of-function mutations in a calcium-  
13 channel alpha1-subunit gene in Xp11.23 cause incomplete X-linked congenital stationary  
14 night blindness. *Nat. Genet.* 19, 264-267.
- 15 Bech-Hansen, N.T., Naylor, M.J., Maybaum, T.A., Sparkes, R.L., Koop, B., Birch, D.G.,  
16 Bergen, A.A., Prinsen, C.F., Polomeno, R.C., Gal, A., Drack, A.V., Musarella, M.A.,  
17 Jacobson, S.G., Young, R.S., Weleber, R.G., 2000. Mutations in NYX, encoding the leucine-  
18 rich proteoglycan nyctalopin, cause X-linked complete congenital stationary night blindness.  
19 *Nat. Genet.* 26, 319-323.
- 20 Beighle, C., Karp, L.E., Hanson, J.W., Hall, J.G., Hoehn, H., 1977. Small structural changes  
21 of chromosome 8. Two cases with evidence for deletion. *Hum. Genet.* 38, 113-121.
- 22 Beighton, P., 1970. Ehlers-Danlos syndrome. *Ann. Rheum. Dis.* 29, 332-333.
- 23 Beleggia, F., Li, Y., Fan, J., Elcioglu, N.H., Toker, E., Wieland, T., Maumenee, I.H., Akarsu,  
24 N.A., Meitinger, T., Strom, T.M., Lang, R., Wollnik, B., 2015. CRIM1 haploinsufficiency  
25 causes defects in eye development in human and mouse. *Hum Mol Genet* 24, 2267-2273.
- 26 Berkley, M.A., Watkins, D.W., 1973. Grating resolution and refraction in the cat estimated  
27 from evoked cerebral potentials. *Vision Res* 13, 403-415.
- 28 Bijveld, M.M., Florijn, R.J., Bergen, A.A., van den Born, L.I., Kamermans, M., Prick, L.,  
29 Riemsdag, F.C., van Schooneveld, M.J., Kappers, A.M., van Genderen, M.M., 2013.  
30 Genotype and phenotype of 101 dutch patients with congenital stationary night blindness.  
31 *Ophthalmology* 120, 2072-2081.
- 32 Blake, R., Cool, S.J., Crawford, M.L., 1974. Visual resolution in the cat. *Vision Res* 14, 1211-  
33 1217.
- 34 Blond, F., Leveillard, T., 2019. Functional Genomics of the Retina to Elucidate its  
35 Construction and Deconstruction. *Int. J. Mol. Sci.* 20.
- 36 Boatright, J.H., Gordon, J.R., Iuvone, P.M., 1994. Inhibition of endogenous dopamine release  
37 in amphibian retina by L-2-amino-4-phosphonobutyric acid (L-AP4) and trans-2-  
38 aminocyclopentane-1,3-dicarboxylate (ACPD). *Brain Res.* 649, 339-342.

1 Boelen, M.K., Boelen, M.G., Marshak, D.W., 1998. Light-stimulated release of dopamine  
2 from the primate retina is blocked by 1-2-amino-4-phosphonobutyric acid (APB). *Vis.*  
3 *Neurosci.* 15, 97-103.

4 Bramall, A.N., Szego, M.J., Pacione, L.R., Chang, I., Diez, E., D'Orleans-Juste, P., Stewart,  
5 D.J., Hauswirth, W.W., Yanagisawa, M., McInnes, R.R., 2013. Endothelin-2-mediated  
6 protection of mutant photoreceptors in inherited photoreceptor degeneration. *PLoS ONE* 8,  
7 e58023.

8 Bramblett, D.E., Pennesi, M.E., Wu, S.M., Tsai, M.J., 2004. The transcription factor *Bhlhb4*  
9 is required for rod bipolar cell maturation. *Neuron* 43, 779-793.

10 Brand, C., Schaeffel, F., Feldkaemper, M.P., 2007. A microarray analysis of retinal transcripts  
11 that are controlled by image contrast in mice. *Mol. Vis.* 13, 920-932.

12 Brandau, O., Aszodi, A., Hunziker, E.B., Neame, P.J., Vestweber, D., Fassler, R., 2002.  
13 Chondromodulin I is dispensable during enchondral ossification and eye development. *Mol.*  
14 *Cell. Biol.* 22, 6627-6635.

15 Brennan, N.A., Toubouti, Y.M., Cheng, X., Bullimore, M.A., 2021. Efficacy in myopia  
16 control. *Prog. Retin. Eye Res.* 83, 100923.

17 Brown, J.L., Snir, M., Noushmehr, H., Kirby, M., Hong, S.K., Elkahoul, A.G., Feldman, B.,  
18 2008. Transcriptional profiling of endogenous germ layer precursor cells identifies *dusp4* as  
19 an essential gene in zebrafish endoderm specification. *Proc Natl Acad Sci U S A* 105, 12337-  
20 12342.

21 Buhot, M.C., Dubayle, D., Malleret, G., Javerzat, S., Segu, L., 2001. Exploration, anxiety, and  
22 spatial memory in transgenic anophthalmic mice. *Behav Neurosci* 115, 455-467.

23 Bui Quoc, E., Milleret, C., 2014. Origins of strabismus and loss of binocular vision. *Front.*  
24 *Integr. Neurosci.* 8, 71.

25 Buttery, R.G., Hinrichsen, C.F., Weller, W.L., Haight, J.R., 1991. How thick should a retina  
26 be? A comparative study of mammalian species with and without intraretinal vasculature.  
27 *Vision Res* 31, 169-187.

28 Cao, Y., Posokhova, E., Martemyanov, K.A., 2011. TRPM1 forms complexes with nyctalopin  
29 in vivo and accumulates in postsynaptic compartment of ON-bipolar neurons in mGluR6-  
30 dependent manner. *J. Neurosci.* 31, 11521-11526.

31 Carr, B.J., Nguyen, C.T., Stell, W.K., 2019. Alpha2 -adrenoceptor agonists inhibit form-  
32 deprivation myopia in the chick. *Clin Exp Optom* 102, 418-425.

33 Cases, O., Joseph, A., Obry, A., Santin, M.D., Ben-Yacoub, S., Paques, M., Amsellem-  
34 Levera, S., Bribian, A., Simonutti, M., Augustin, S., Debeir, T., Sahel, J.A., Christ, A., de  
35 Castro, F., Lehericy, S., Cosette, P., Kozyraki, R., 2015. Foxg1-Cre Mediated Lrp2  
36 Inactivation in the Developing Mouse Neural Retina, Ciliary and Retinal Pigment Epithelia  
37 Models Congenital High Myopia. *PLoS ONE* 10, e0129518.



- 1 Casson, R.J., Kahawita, S., Kong, A., Muecke, J., Sisaleumsak, S., Visonnavong, V., 2012.  
2 Exceptionally low prevalence of refractive error and visual impairment in schoolchildren from  
3 Lao People's Democratic Republic. *Ophthalmology* 119, 2021-2027.
- 4 Chakraborty, R., Lacy, K.D., Tan, C.C., Park, H.N., Pardue, M.T., 2014a. Refractive index  
5 measurement of the mouse crystalline lens using optical coherence tomography. *Exp. Eye*  
6 *Res.* 125, 62-70.
- 7 Chakraborty, R., Ostrin, L.A., Nickla, D.L., Iuvone, P.M., Pardue, M.T., Stone, R.A., 2018.  
8 Circadian rhythms, refractive development, and myopia. *Ophthalmic Physiol. Opt.* 38, 217-  
9 245.
- 10 Chakraborty, R., Park, H., Aung, M.H., Tan, C.C., Sidhu, C.S., Iuvone, P.M., Pardue, M.T.,  
11 2014b. Comparison of refractive development and retinal dopamine in OFF pathway mutant  
12 and C57BL/6J wild-type mice. *Mol. Vis.* 20, 1318-1327.
- 13 Chakraborty, R., Park, H.N., Hanif, A.M., Sidhu, C.S., Iuvone, P.M., Pardue, M.T., 2015. ON  
14 pathway mutations increase susceptibility to form-deprivation myopia. *Exp. Eye Res.* 137, 79-  
15 83.
- 16 Chebib, M., Hinton, T., Schmid, K.L., Brinkworth, D., Qian, H., Matos, S., Kim, H.L., Abdel-  
17 Halim, H., Kumar, R.J., Johnston, G.A., Hanrahan, J.R., 2009. Novel, potent, and selective  
18 GABAC antagonists inhibit myopia development and facilitate learning and memory. *J.*  
19 *Pharmacol. Exp. Ther.* 328, 448-457.
- 20 Chen, B.Y., Wang, C.Y., Chen, W.Y., Ma, J.X., 2013. Altered TGF-beta2 and bFGF  
21 expression in scleral desmocytes from an experimentally-induced myopia guinea pig model.  
22 *Graefes Arch Clin Exp Ophthalmol* 251, 1133-1144.
- 23 Chen, L., Wu, W., Dentchev, T., Zeng, Y., Wang, J., Tsui, I., Tobias, J.W., Bennett, J.,  
24 Baldwin, D., Dunaief, J.L., 2004. Light damage induced changes in mouse retinal gene  
25 expression. *Exp. Eye Res.* 79, 239-247.
- 26 Cheng, Z.Y., Chebib, M., Schmid, K.L., 2011. rho1 GABAC receptors are expressed in  
27 fibrous and cartilaginous layers of chick sclera and located on sclera fibroblasts and  
28 chondrocytes. *J. Neurochem.* 118, 281-287.
- 29 Cheng, Z.Y., Wang, X.P., Schmid, K.L., Han, X.G., 2014. Inhibition of form-deprivation  
30 myopia by a GABA<sub>A</sub> receptor antagonist, (1,2,5,6-tetrahydropyridin-4-yl)  
31 methylphosphinic acid (TPMPA), in guinea pigs. *Graefes Arch Clin Exp Ophthalmol* 252,  
32 1939-1946.
- 33 Chilcote, R.R., Le Beau, M.M., Dampier, C., Pergament, E., Verlinsky, Y., Mohandas, N.,  
34 Frischer, H., Rowley, J.D., 1987. Association of red cell spherocytosis with deletion of the  
35 short arm of chromosome 8. *Blood* 69, 156-159.
- 36 Chirivi, R.G., Noordman, Y.E., Van der Zee, C.E., Hendriks, W.J., 2007. Altered MAP kinase  
37 phosphorylation and impaired motor coordination in PTPRR deficient mice. *J. Neurochem.*  
38 101, 829-840.
- 39 Christodoulou, E., Rashid, M., Pacini, C., Droop, A., Robertson, H., Groningen, T.V.,  
40 Teunisse, A., Iorio, F., Jochemsen, A.G., Adams, D.J., Doorn, R.V., 2021. Analysis of

1 CRISPR-Cas9 screens identifies genetic dependencies in melanoma. *Pigment Cell Melanoma*  
2 *Res.* 34, 122-131.

3 Chu, P.H.W., Chan, H.H.L., Ng, Y.F., Brown, B., Siu, A.W., Beale, B.A., Gilger, B.C.,  
4 Wong, F., 2008. Porcine global flash multifocal electroretinogram: possible mechanisms for  
5 the glaucomatous changes in contrast response function. *Vision Res.* 48, 1726-1734.

6 Cirelli, C., Tononi, G., 2000. Differential expression of plasticity-related genes in waking and  
7 sleep and their regulation by the noradrenergic system. *J. Neurosci.* 20, 9187-9194.

8 Cook, M.N., Williams, R.W., Flaherty, L., 2001. Anxiety-related behaviors in the elevated  
9 zero-maze are affected by genetic factors and retinal degeneration. *Behav Neurosci* 115, 468-  
10 476.

11 Costa, C., Gimenez-Capitan, A., Karachaliou, N., Rosell, R., 2013. Comprehensive molecular  
12 screening: from the RT-PCR to the RNA-seq. *Transl Lung Cancer Res* 2, 87-91.

13 Cottet, S., Michaut, L., Boisset, G., Schlecht, U., Gehring, W., Schorderet, D.F., 2006.  
14 Biological characterization of gene response in Rpe65<sup>-/-</sup> mouse model of Leber's congenital  
15 amaurosis during progression of the disease. *FASEB J* 20, 2036-2049.

16 Cumberland, P.M., Bao, Y., Hysi, P.G., Foster, P.J., Hammond, C.J., Rahi, J.S., Eyes, U.K.B.,  
17 Vision, C., 2015. Frequency and Distribution of Refractive Error in Adult Life: Methodology  
18 and Findings of the UK Biobank Study. *PLoS ONE* 10, e0139780.

19 Cutting, G.R., Lu, L., O'Hara, B.F., Kasch, L.M., Montrose-Rafizadeh, C., Donovan, D.M.,  
20 Shimada, S., Antonarakis, S.E., Guggino, W.B., Uhl, G.R., et al., 1991. Cloning of the  
21 gamma-aminobutyric acid (GABA) rho 1 cDNA: a GABA receptor subunit highly expressed  
22 in the retina. *Proc Natl Acad Sci U S A* 88, 2673-2677.

23 Dandona, R., Dandona, L., Srinivas, M., Giridhar, P., McCarty, C.A., Rao, G.N., 2002a.  
24 Population-based assessment of refractive error in India: the Andhra Pradesh eye disease  
25 study. *Clin Exp Ophthalmol* 30, 84-93.

26 Dandona, R., Dandona, L., Srinivas, M., Sahare, P., Narsaiah, S., Munoz, S.R., Pokharel,  
27 G.P., Ellwein, L.B., 2002b. Refractive error in children in a rural population in India. *Invest*  
28 *Ophthalmol Vis Sci* 43, 615-622.

29 Daw, N.W., Brunken, W.J., Parkinson, D., 1989. The function of synaptic transmitters in the  
30 retina. *Annu. Rev. Neurosci.* 12, 205-225.

31 de la Cera, E.G., Rodriguez, G., Llorente, L., Schaeffel, F., Marcos, S., 2006. Optical  
32 aberrations in the mouse eye. *Vision Res* 46, 2546-2553.

33 Devriendt, K., Matthijs, G., Van Dael, R., Gewillig, M., Eyskens, B., Hjalgrim, H., Dolmer,  
34 B., McGaughan, J., Brondum-Nielsen, K., Marynen, P., Fryns, J.P., Vermeesch, J.R., 1999.  
35 Delineation of the critical deletion region for congenital heart defects, on chromosome  
36 8p23.1. *Am. J. Hum. Genet.* 64, 1119-1126.

37 Dhingra, A., Sulaiman, P., Xu, Y., Fina, M.E., Veh, R.W., Vardi, N., 2008. Probing  
38 neurochemical structure and function of retinal ON bipolar cells with a transgenic mouse. *J.*  
39 *Comp. Neurol.* 510, 484-496.

1 Di Schiavi, E., Riano, E., Heye, B., Bazzicalupo, P., Rugarli, E.I., 2005. UMODL1/Olfactorin  
2 is an extracellular membrane-bound molecule with a restricted spatial expression in olfactory  
3 and vomeronasal neurons. *Eur. J. Neurosci.* 21, 3291-3300.

4 Dickinson, R.J., Keyse, S.M., 2006. Diverse physiological functions for dual-specificity MAP  
5 kinase phosphatases. *J. Cell Sci.* 119, 4607-4615.

6 Dirani, M., Chamberlain, M., Shekar, S.N., Islam, A.F., Garoufalidis, P., Chen, C.Y., Guymer,  
7 R.H., Baird, P.N., 2006. Heritability of refractive error and ocular biometrics: the Genes in  
8 Myopia (GEM) twin study. *Invest Ophthalmol Vis Sci* 47, 4756-4761.

9 Doi, M., Ishida, A., Miyake, A., Sato, M., Komatsu, R., Yamazaki, F., Kimura, I., Tsuchiya,  
10 S., Kori, H., Seo, K., Yamaguchi, Y., Matsuo, M., Fustin, J.M., Tanaka, R., Santo, Y.,  
11 Yamada, H., Takahashi, Y., Araki, M., Nakao, K., Aizawa, S., Kobayashi, M., Obrietan, K.,  
12 Tsujimoto, G., Okamura, H., 2011. Circadian regulation of intracellular G-protein signalling  
13 mediates intercellular synchrony and rhythmicity in the suprachiasmatic nucleus. *Nat.*  
14 *Commun.* 2, 327.

15 Drager, U.C., Olsen, J.F., 1981. Ganglion cell distribution in the retina of the mouse. *Invest*  
16 *Ophthalmol Vis Sci* 20, 285-293.

17 Dryja, T.P., McGee, T.L., Berson, E.L., Fishman, G.A., Sandberg, M.A., Alexander, K.R.,  
18 Derlacki, D.J., Rajagopalan, A.S., 2005. Night blindness and abnormal cone  
19 electroretinogram ON responses in patients with mutations in the GRM6 gene encoding  
20 mGluR6. *Proc Natl Acad Sci U S A* 102, 4884-4889.

21 Dumitrescu, O.N., Pucci, F.G., Wong, K.Y., Berson, D.M., 2009. Ectopic retinal ON bipolar  
22 cell synapses in the OFF inner plexiform layer: contacts with dopaminergic amacrine cells  
23 and melanopsin ganglion cells. *J. Comp. Neurol.* 517, 226-244.

24 Dunlap, J.C., 1999. Molecular bases for circadian clocks. *Cell* 96, 271-290.

25 Dynes, J.L., Steward, O., 2007. Dynamics of bidirectional transport of Arc mRNA in neuronal  
26 dendrites. *J. Comp. Neurol.* 500, 433-447.

27 Ehrlich, D., Sattayasai, J., Zappia, J., Barrington, M., 1990. Effects of selective neurotoxins  
28 on eye growth in the young chick. *Ciba Found. Symp.* 155, 63-84; discussion 84-68.

29 Elbaz, A., Vale-Santos, J., Jurkat-Rott, K., Lapie, P., Ophoff, R.A., Bady, B., Links, T.P.,  
30 Piussan, C., Vila, A., Monnier, N., et al., 1995. Hypokalemic periodic paralysis and the  
31 dihydropyridine receptor (CACNL1A3): genotype/phenotype correlations for two  
32 predominant mutations and evidence for the absence of a founder effect in 16 caucasian  
33 families. *Am. J. Hum. Genet.* 56, 374-380.

34 Enz, R., 2001. GABA(C) receptors: a molecular view. *Biol. Chem.* 382, 1111-1122.

35 Fan, Q., Verhoeven, V.J., Wojciechowski, R., Barathi, V.A., Hysi, P.G., Guggenheim, J.A.,  
36 Hohn, R., Vitart, V., Khawaja, A.P., Yamashiro, K., Hosseini, S.M., Lehtimäki, T., Lu, Y.,  
37 Haller, T., Xie, J., Delcourt, C., Pirastu, M., Wedenoja, J., Gharahkhani, P., Venturini, C.,  
38 Miyake, M., Hewitt, A.W., Guo, X., Mazur, J., Huffman, J.E., Williams, K.M., Polasek, O.,  
39 Campbell, H., Rudan, I., Vataavuk, Z., Wilson, J.F., Joshi, P.K., McMahon, G., St Pourcain,  
40 B., Evans, D.M., Simpson, C.L., Schwantes-An, T.H., Igo, R.P., Mirshahi, A., Cougnard-

1 Gregoire, A., Bellenguez, C., Blettner, M., Raitakari, O., Kahonen, M., Seppala, I., Zeller, T.,  
2 Meitinger, T., Consortium for Refractive, E., Myopia, Ried, J.S., Gieger, C., Portas, L., van  
3 Leeuwen, E.M., Amin, N., Uitterlinden, A.G., Rivadeneira, F., Hofman, A., Vingerling, J.R.,  
4 Wang, Y.X., Wang, X., Tai-Hui Boh, E., Ikram, M.K., Sabanayagam, C., Gupta, P., Tan, V.,  
5 Zhou, L., Ho, C.E., Lim, W., Beuerman, R.W., Siantar, R., Tai, E.S., Vithana, E., Mihailov,  
6 E., Khor, C.C., Hayward, C., Luben, R.N., Foster, P.J., Klein, B.E., Klein, R., Wong, H.S.,  
7 Mitchell, P., Metspalu, A., Aung, T., Young, T.L., He, M., Parssinen, O., van Duijn, C.M., Jin  
8 Wang, J., Williams, C., Jonas, J.B., Teo, Y.Y., Mackey, D.A., Oexle, K., Yoshimura, N.,  
9 Paterson, A.D., Pfeiffer, N., Wong, T.Y., Baird, P.N., Stambolian, D., Wilson, J.E., Cheng,  
10 C.Y., Hammond, C.J., Klaver, C.C., Saw, S.M., Rahi, J.S., Korobelnik, J.F., Kemp, J.P.,  
11 Timpson, N.J., Smith, G.D., Craig, J.E., Burdon, K.P., Fogarty, R.D., Iyengar, S.K., Chew, E.,  
12 Janmahasatian, S., Martin, N.G., MacGregor, S., Xu, L., Schache, M., Nangia, V., Panda-  
13 Jonas, S., Wright, A.F., Fondran, J.R., Lass, J.H., Feng, S., Zhao, J.H., Khaw, K.T.,  
14 Wareham, N.J., Rantanen, T., Kaprio, J., Pang, C.P., Chen, L.J., Tam, P.O., Jhanji, V.,  
15 Young, A.L., Doring, A., Raffel, L.J., Cotch, M.F., Li, X., Yip, S.P., Yap, M.K., Biino, G.,  
16 Vaccargiu, S., Fossarello, M., Fleck, B., Yazar, S., Tideman, J.W., Tedja, M., Deangelis,  
17 M.M., Morrison, M., Farrer, L., Zhou, X., Chen, W., Mizuki, N., Meguro, A., Makela, K.M.,  
18 2016. Meta-analysis of gene-environment-wide association scans accounting for education  
19 level identifies additional loci for refractive error. *Nat. Commun.* 7, 11008.

20 Farkas, M.H., Grant, G.R., White, J.A., Sousa, M.E., Consugar, M.B., Pierce, E.A., 2013.  
21 Transcriptome analyses of the human retina identify unprecedented transcript diversity and  
22 3.5 Mb of novel transcribed sequence via significant alternative splicing and novel genes.  
23 *BMC Genomics* 14, 486.

24 Fauchoux, C., Naye, F., Treguer, K., Fedou, S., Thiebaud, P., Theze, N., 2010. Vestigial like  
25 gene family expression in *Xenopus*: common and divergent features with other vertebrates.  
26 *Int. J. Dev. Biol.* 54, 1375-1382.

27 Faulstich, B.M., Onori, K.A., du Lac, S., 2004. Comparison of plasticity and development of  
28 mouse optokinetic and vestibulo-ocular reflexes suggests differential gain control  
29 mechanisms. *Vision Res* 44, 3419-3427.

30 Fichard, A., Kleman, J.P., Ruggiero, F., 1995. Another look at collagen V and XI molecules.  
31 *Matrix Biol.* 14, 515-531.

32 Fischer, A.J., Morgan, I.G., Stell, W.K., 1999. Colchicine causes excessive ocular growth and  
33 myopia in chicks. *Vision Res.* 39, 685-697.

34 Flaxel, C.J., Jay, M., Thiselton, D.L., Nayudu, M., Hardcastle, A.J., Wright, A., Bird, A.C.,  
35 1999. Difference between RP2 and RP3 phenotypes in X linked retinitis pigmentosa. *Br. J.*  
36 *Ophthalmol.* 83, 1144-1148.

37 Flitcroft, D.I., 2012. The complex interactions of retinal, optical and environmental factors in  
38 myopia aetiology. *Prog. Retin. Eye Res.* 31, 622-660.

39 Flitcroft, D.I., He, M., Jonas, J.B., Jong, M., Naidoo, K., Ohno-Matsui, K., Rahi, J.,  
40 Resnikoff, S., Vitale, S., Yannuzzi, L., 2019. IMI - Defining and Classifying Myopia: A  
41 Proposed Set of Standards for Clinical and Epidemiologic Studies. *Invest Ophthalmol Vis Sci*  
42 60, M20-M30.

- 1 Flitcroft, D.I., Loughman, J., Wildsoet, C.F., Williams, C., Guggenheim, J.A., Consortium,  
2 C., 2018. Novel Myopia Genes and Pathways Identified From Syndromic Forms of Myopia.  
3 *Invest Ophthalmol Vis Sci* 59, 338-348.
- 4 Flores, A.E., Flores, J.E., Deshpande, H., Picazo, J.A., Xie, X.S., Franken, P., Heller, H.C.,  
5 Grahn, D.A., O'Hara, B.F., 2007. Pattern recognition of sleep in rodents using piezoelectric  
6 signals generated by gross body movements. *IEEE Trans Biomed Eng* 54, 225-233.
- 7 Foster, P.J., Jiang, Y., 2014. Epidemiology of myopia. *Eye (Lond)* 28, 202-208.
- 8 French, A.N., Morgan, I.G., Burlutsky, G., Mitchell, P., Rose, K.A., 2013. Prevalence and 5-  
9 to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren.  
10 *Ophthalmology* 120, 1482-1491.
- 11 Frost, M.R., Norton, T.T., 2012. Alterations in protein expression in tree shrew sclera during  
12 development of lens-induced myopia and recovery. *Invest Ophthalmol Vis Sci* 53, 322-336.
- 13 Fujikado, T., Kawasaki, Y., Suzuki, A., Ohmi, G., Tano, Y., 1997. Retinal function with lens-  
14 induced myopia compared with form-deprivation myopia in chicks. *Graefes Arch Clin Exp*  
15 *Ophthalmol* 235, 320-324.
- 16 Funaki, H., Sawaguchi, S., Yaoeda, K., Koyama, Y., Yaoita, E., Funaki, S., Shirakashi, M.,  
17 Oshima, Y., Shukunami, C., Hiraki, Y., Abe, H., Yamamoto, T., 2001. Expression and  
18 localization of angiogenic inhibitory factor, chondromodulin-I, in adult rat eye. *Invest*  
19 *Ophthalmol Vis Sci* 42, 1193-1200.
- 20 Gao, H., Frost, M.R., Siegwart, J.T., Jr., Norton, T.T., 2011. Patterns of mRNA and protein  
21 expression during minus-lens compensation and recovery in tree shrew sclera. *Mol. Vis.* 17,  
22 903-919.
- 23 Gao, Q., Liu, Q., Ma, P., Zhong, X., Wu, J., Ge, J., 2006. Effects of direct intravitreal  
24 dopamine injections on the development of lid-suture induced myopia in rabbits. *Graefes*  
25 *Arch Clin Exp Ophthalmol* 244, 1329-1335.
- 26 Gao, Z., Meng, N., Muecke, J., Chan, W.O., Piseth, H., Kong, A., Jnguyenphamhh, T.,  
27 Dehghan, Y., Selva, D., Casson, R., Ang, K., 2012. Refractive error in school children in an  
28 urban and rural setting in Cambodia. *Ophthalmic Epidemiol.* 19, 16-22.
- 29 Gehrig, A., Langmann, T., Horling, F., Janssen, A., Bonin, M., Walter, M., Poths, S., Weber,  
30 B.H., 2007. Genome-wide expression profiling of the retinoschisin-deficient retina in early  
31 postnatal mouse development. *Invest Ophthalmol Vis Sci* 48, 891-900.
- 32 Gharbiya, M., Moramarco, A., Castori, M., Parisi, F., Celletti, C., Marengo, M., Mariani, I.,  
33 Grammatico, P., Camerota, F., 2012. Ocular features in joint hypermobility syndrome/ehlers-  
34 danlos syndrome hypermobility type: a clinical and in vivo confocal microscopy study. *Am. J.*  
35 *Ophthalmol.* 154, 593-600 e591.
- 36 Gibbs, M.E., Johnston, G.A., 2005. Opposing roles for GABAA and GABAC receptors in  
37 short-term memory formation in young chicks. *Neuroscience* 131, 567-576.
- 38 Godara, P., Cooper, R.F., Sergouniotis, P.I., Diederichs, M.A., Streb, M.R., Genead, M.A.,  
39 McAnany, J.J., Webster, A.R., Moore, A.T., Dubis, A.M., Neitz, M., Dubra, A., Stone, E.M.,

1 Fishman, G.A., Han, D.P., Michaelides, M., Carroll, J., 2012. Assessing retinal structure in  
2 complete congenital stationary night blindness and Oguchi disease. *Am. J. Ophthalmol.* 154,  
3 987-1001 e1001.

4 Goss, D.A., Wickham, M.G., 1995. Retinal-image mediated ocular growth as a mechanism  
5 for juvenile onset myopia and for emmetropization. A literature review. *Doc. Ophthalmol.* 90,  
6 341-375.

7 Graw, J., 2010. Eye development. *Curr. Top. Dev. Biol.* 90, 343-386.

8 Gregg, R.G., Mukhopadhyay, S., Candille, S.I., Ball, S.L., Pardue, M.T., McCall, M.A.,  
9 Peachey, N.S., 2003. Identification of the gene and the mutation responsible for the mouse  
10 nob phenotype. *Invest Ophthalmol Vis Sci* 44, 378-384.

11 Grinchuk, O., Kozmik, Z., Wu, X., Tomarev, S., 2005. The Optomedin gene is a downstream  
12 target of Pax6. *J Biol Chem* 280, 35228-35237.

13 Guan, K.L., Butch, E., 1995. Isolation and characterization of a novel dual specific  
14 phosphatase, HVH2, which selectively dephosphorylates the mitogen-activated protein  
15 kinase. *J Biol Chem* 270, 7197-7203.

16 Gurlevik, U., Kara, H., Yasar, E., 2021. Effect of methylphenidate as a dopaminergic agent on  
17 myopia: Pilot study. *Int. J. Clin. Pract.* 75, e14665.

18 Hammond, C.J., Snieder, H., Gilbert, C.E., Spector, T.D., 2001. Genes and environment in  
19 refractive error: the twin eye study. *Invest Ophthalmol Vis Sci* 42, 1232-1236.

20 Hasan, N., Pangen, G., Cobb, C.A., Ray, T.A., Nettesheim, E.R., Ertel, K.J., Lipinski, D.M.,  
21 McCall, M.A., Gregg, R.G., 2019. Presynaptic Expression of LRIT3 Transsynaptically  
22 Organizes the Postsynaptic Glutamate Signaling Complex Containing TRPM1. *Cell Rep* 27,  
23 3107-3116 e3103.

24 Hasan, N., Pangen, G., Ray, T.A., Fransen, K.M., Noel, J., Borghuis, B.G., McCall, M.A.,  
25 Gregg, R.G., 2020. LRIT3 is Required for Nyctalopin Expression and Normal ON and OFF  
26 Pathway Signaling in the Retina. *eNeuro* 7.

27 Hasan, N., Ray, T.A., Gregg, R.G., 2016. CACNA1S expression in mouse retina: Novel  
28 isoforms and antibody cross-reactivity with GPR179. *Vis. Neurosci.* 33, E009.

29 Hawthorne, F., Feng, S., Metlapally, R., Li, Y.J., Tran-Viet, K.N., Guggenheim, J.A.,  
30 Malecaze, F., Calvas, P., Rosenberg, T., Mackey, D.A., Venturini, C., Hysi, P.G., Hammond,  
31 C.J., Young, T.L., 2013. Association mapping of the high-grade myopia MYP3 locus reveals  
32 novel candidates UHRF1BP1L, PTPRR, and PPFIA2. *Invest Ophthalmol Vis Sci* 54, 2076-  
33 2086.

34 He, M., Xiang, F., Zeng, Y., Mai, J., Chen, Q., Zhang, J., Smith, W., Rose, K., Morgan, I.G.,  
35 2015. Effect of Time Spent Outdoors at School on the Development of Myopia Among  
36 Children in China: A Randomized Clinical Trial. *JAMA* 314, 1142-1148.

37 Herzog, K.H., von Bartheld, C.S., 1998. Contributions of the optic tectum and the retina as  
38 sources of brain-derived neurotrophic factor for retinal ganglion cells in the chick embryo. *J.*  
39 *Neurosci.* 18, 2891-2906.

- 1 Histed, M.H., Carvalho, L.A., Maunsell, J.H., 2012. Psychophysical measurement of contrast  
2 sensitivity in the behaving mouse. *Journal of neurophysiology* 107, 758-765.
- 3 Ho, W.C., Wong, O.Y., Chan, Y.C., Wong, S.W., Kee, C.S., Chan, H.H., 2012. Sign-  
4 dependent changes in retinal electrical activity with positive and negative defocus in the  
5 human eye. *Vision Res.* 52, 47-53.
- 6 Hoek, K.S., Schlegel, N.C., Eichhoff, O.M., Widmer, D.S., Praetorius, C., Einarsson, S.O.,  
7 Valgeirsdottir, S., Bergsteinsdottir, K., Schepsky, A., Dummer, R., Steingrimsson, E., 2008.  
8 Novel MITF targets identified using a two-step DNA microarray strategy. *Pigment Cell*  
9 *Melanoma Res.* 21, 665-676.
- 10 Holden, B., Sankaridurg, P., Smith, E., Aller, T., Jong, M., He, M., 2014. Myopia, an  
11 underrated global challenge to vision: where the current data takes us on myopia control. *Eye*  
12 *(Lond)* 28, 142-146.
- 13 Holden, B.A., Fricke, T.R., Wilson, D.A., Jong, M., Naidoo, K.S., Sankaridurg, P., Wong,  
14 T.Y., Naduvilath, T.J., Resnikoff, S., 2016. Global Prevalence of Myopia and High Myopia  
15 and Temporal Trends from 2000 through 2050. *Ophthalmology* 123, 1036-1042.
- 16 Hornbeak, D.M., Young, T.L., 2009. Myopia genetics: a review of current research and  
17 emerging trends. *Curr. Opin. Ophthalmol.* 20, 356-362.
- 18 Horvat-Brocker, A., Reinhard, J., Illes, S., Paech, T., Zoidl, G., Harroch, S., Distler, C.,  
19 Knyazev, P., Ullrich, A., Faissner, A., 2008. Receptor protein tyrosine phosphatases are  
20 expressed by cycling retinal progenitor cells and involved in neuronal development of mouse  
21 retina. *Neuroscience* 152, 618-645.
- 22 Howlett, M.H., McFadden, S.A., 2007. Emmetropization and schematic eye models in  
23 developing pigmented guinea pigs. *Vision Res* 47, 1178-1190.
- 24 Hu, Y., Shmygelska, A., Tran, D., Eriksson, N., Tung, J.Y., Hinds, D.A., 2016. GWAS of  
25 89,283 individuals identifies genetic variants associated with self-reporting of being a  
26 morning person. *Nat. Commun.* 7, 10448.
- 27 Hudson, D.M., Joeng, K.S., Werther, R., Rajagopal, A., Weis, M., Lee, B.H., Eyre, D.R.,  
28 2015. Post-translationally abnormal collagens of prolyl 3-hydroxylase-2 null mice offer a  
29 pathobiological mechanism for the high myopia linked to human LEPREL1 mutations. *J Biol*  
30 *Chem* 290, 8613-8622.
- 31 Hull, C., Studholme, K., Yazulla, S., von Gersdorff, H., 2006. Diurnal changes in exocytosis  
32 and the number of synaptic ribbons at active zones of an ON-type bipolar cell terminal. *J*  
33 *Neurophysiol* 96, 2025-2033.
- 34 Hysi, P.G., Choquet, H., Khawaja, A.P., Wojciechowski, R., Tedja, M.S., Yin, J., Simcoe,  
35 M.J., Patasova, K., Mahroo, O.A., Thai, K.K., Cumberland, P.M., Melles, R.B., Verhoeven,  
36 V.J.M., Vitart, V., Segre, A., Stone, R.A., Wareham, N., Hewitt, A.W., Mackey, D.A.,  
37 Klaver, C.C.W., MacGregor, S., Consortium for Refractive, E., Myopia, Khaw, P.T., Foster,  
38 P.J., Eye, U.K., Vision, C., Guggenheim, J.A., andMe, I., Rahi, J.S., Jorgenson, E.,  
39 Hammond, C.J., 2020. Meta-analysis of 542,934 subjects of European ancestry identifies new  
40 genes and mechanisms predisposing to refractive error and myopia. *Nat. Genet.* 52, 401-407.

1 Hysi, P.G., Wojciechowski, R., Rahi, J.S., Hammond, C.J., 2014. Genome-wide association  
2 studies of refractive error and myopia, lessons learned, and implications for the future. *Invest*  
3 *Ophthalmol Vis Sci* 55, 3344-3351.

4 Ikeda, S.R., 2001. Signal transduction. Calcium channels--link locally, act globally. *Science*  
5 294, 318-319.

6 Iribarren, R., 2015. Crystalline lens and refractive development. *Prog. Retin. Eye Res.* 47, 86-  
7 106.

8 Irving, E.L., Sivak, J.G., Curry, T.A., Callender, M.G., 1996. Chick eye optics: zero to  
9 fourteen days. *J Comp Physiol A* 179, 185-194.

10 Isidor, B., Pichon, O., Redon, R., Day-Salvatore, D., Hamel, A., Siwicka, K.A., Bitner-  
11 Glindzicz, M., Heymann, D., Kjellen, L., Kraus, C., Leroy, J.G., Mortier, G.R., Rauch, A.,  
12 Verloes, A., David, A., Le Caignec, C., 2010. Mesomelia-synostoses syndrome results from  
13 deletion of SULF1 and SLCO5A1 genes at 8q13. *Am. J. Hum. Genet.* 87, 95-100.

14 Iuvone, P.M., Galli, C.L., Garrison-Gund, C.K., Neff, N.H., 1978. Light stimulates tyrosine  
15 hydroxylase activity and dopamine synthesis in retinal amacrine neurons. *Science* 202, 901-  
16 902.

17 Iuvone, P.M., Tigges, M., Stone, R.A., Lambert, S., Laties, A.M., 1991. Effects of  
18 apomorphine, a dopamine receptor agonist, on ocular refraction and axial elongation in a  
19 primate model of myopia. *Invest Ophthalmol Vis Sci* 32, 1674-1677.

20 Ivanova, M.E., Zolnikova, I.V., Gorgisheli, K.V., Atarshchikov, D.S., Ghosh, P., Barh, D.,  
21 2019. Novel frameshift mutation in NYX gene in a Russian family with complete congenital  
22 stationary night blindness. *Ophthalmic Genet.* 40, 558-563.

23 Jacobs, G.H., 2013. Losses of functional opsin genes, short-wavelength cone photopigments,  
24 and color vision-A significant trend in the evolution of mammalian vision. *Vis Neurosci*, 1-  
25 15.

26 Jarvis, J.R., Abeyesinghe, S.M., McMahon, C.E., Wathes, C.M., 2009. Measuring and  
27 modelling the spatial contrast sensitivity of the chicken (*Gallus g. domesticus*). *Vision Res* 49,  
28 1448-1454.

29 Jellali, A., Meziane, H., Ouagazzal, A.-M., Rousseau, S., Romand, R., Auwerx, J., Sahel, J.-  
30 A., Chambon, P., Picaud, S., 2005. The optomotor response: a robust first-line visual  
31 screening method for mice. *Vision Res.* 45, 1439-1446.

32 Jeon, C.J., Strettoi, E., Masland, R.H., 1998. The major cell populations of the mouse retina. *J*  
33 *Neurosci* 18, 8936-8946.

34 Jia, Y., Hu, D.N., Zhou, J., 2014. Human aqueous humor levels of TGF- beta2: relationship  
35 with axial length. *Biomed Res Int* 2014, 258591.

36 Jiang, X., Xu, Z., Soorma, T., Tariq, A., Bhatti, T., Baneke, A.J., Pontikos, N., Leo, S.M.,  
37 Webster, A.R., Williams, K.M., Hammond, C.J., Hysi, P.G., Mahroo, O.A., 2022. Electrical  
38 responses from human retinal cone pathways associate with a common genetic polymorphism  
39 implicated in myopia. *Proc Natl Acad Sci U S A* 119, e2119675119.



1 Jiao, Y., Yan, J., Zhao, Y., Donahue, L.R., Beamer, W.G., Li, X., Roe, B.A., Ledoux, M.S.,  
2 Gu, W., 2005. Carbonic anhydrase-related protein VIII deficiency is associated with a  
3 distinctive lifelong gait disorder in waddles mice. *Genetics* 171, 1239-1246.

4 Jimenez, J.R., Bermudez, J., Rubino, M., Gomez, L., Anera, R.G., 2004. Prevalence of  
5 myopia in an adult population of two different ethnic groups in the Ecuadorian Amazon. *Jpn.*  
6 *J. Ophthalmol.* 48, 163-165.

7 Jimenez, R., Soler, M., Anera, R.G., Castro, J.J., Perez, M.A., Salas, C., 2012. Ametropias in  
8 school-age children in Fada N'Gourma (Burkina Faso, Africa). *Optom. Vis. Sci.* 89, 33-37.

9 Jin, Z.B., Wu, J., Huang, X.F., Feng, C.Y., Cai, X.B., Mao, J.Y., Xiang, L., Wu, K.C., Xiao,  
10 X., Kloss, B.A., Li, Z., Liu, Z., Huang, S., Shen, M., Cheng, F.F., Cheng, X.W., Zheng, Z.L.,  
11 Chen, X., Zhuang, W., Zhang, Q., Young, T.L., Xie, T., Lu, F., Qu, J., 2017. Trio-based  
12 exome sequencing arrests de novo mutations in early-onset high myopia. *Proc Natl Acad Sci*  
13 *U S A* 114, 4219-4224.

14 Jobling, A.I., Nguyen, M., Gentle, A., McBrien, N.A., 2004. Isoform-specific changes in  
15 scleral transforming growth factor-beta expression and the regulation of collagen synthesis  
16 during myopia progression. *J Biol Chem* 279, 18121-18126.

17 Kalathur, R.K., Gagniere, N., Berthommier, G., Poidevin, L., Raffelsberger, W., Ripp, R.,  
18 Leveillard, T., Poch, O., 2008. RETINOBASE: a web database, data mining and analysis  
19 platform for gene expression data on retina. *BMC Genomics* 9, 208.

20 Kantarci, S., Al-Gazali, L., Hill, R.S., Donnai, D., Black, G.C., Bieth, E., Chassaing, N.,  
21 Lacombe, D., Devriendt, K., Teebi, A., Loscertales, M., Robson, C., Liu, T., MacLaughlin,  
22 D.T., Noonan, K.M., Russell, M.K., Walsh, C.A., Donahoe, P.K., Pober, B.R., 2007.  
23 Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow  
24 and facio-oculo-acoustico-renal syndromes. *Nat. Genet.* 39, 957-959.

25 Kato, K., 1990. Sequence of a novel carbonic anhydrase-related polypeptide and its exclusive  
26 presence in Purkinje cells. *FEBS Lett.* 271, 137-140.

27 Kempen, J.H., Mitchell, P., Lee, K.E., Tielsch, J.M., Broman, A.T., Taylor, H.R., Ikram,  
28 M.K., Congdon, N.G., O'Colmain, B.J., Eye Diseases Prevalence Research, G., 2004. The  
29 prevalence of refractive errors among adults in the United States, Western Europe, and  
30 Australia. *Arch. Ophthalmol.* 122, 495-505.

31 Khandekar, R.B., Abdu-Helmi, S., 2004. Magnitude and determinants of refractive error in  
32 Omani school children. *Saudi medical journal* 25, 1388-1393.

33 Kiefer, A.K., Tung, J.Y., Do, C.B., Hinds, D.A., Mountain, J.L., Francke, U., Eriksson, N.,  
34 2013. Genome-wide analysis points to roles for extracellular matrix remodeling, the visual  
35 cycle, and neuronal development in myopia. *PLoS Genet* 9, e1003299.

36 Kim, S.D., Liu, J.L., Roscioli, T., Buckley, M.F., Yagnik, G., Boyadjiev, S.A., Kim, J., 2012.  
37 Leucine-rich repeat, immunoglobulin-like and transmembrane domain 3 (LRIT3) is a  
38 modulator of FGFR1. *FEBS Lett.* 586, 1516-1521.

39 Klocker, N., Kermer, P., Weishaupt, J.H., Labes, M., Ankerhold, R., Bahr, M., 2000. Brain-  
40 derived neurotrophic factor-mediated neuroprotection of adult rat retinal ganglion cells in

1 vivo does not exclusively depend on phosphatidyl-inositol-3'-kinase/protein kinase B  
2 signaling. *J. Neurosci.* 20, 6962-6967.

3 Klopocki, E., Fiebig, B., Robinson, P., Tonnies, H., Erdogan, F., Ropers, H.H., Mundlos, S.,  
4 Ullmann, R., 2006. A novel 8 Mb interstitial deletion of chromosome 8p12-p21.2. *Am. J.*  
5 *Med. Genet. A.* 140, 873-877.

6 Ko, G.Y., Shi, L., Ko, M.L., 2009. Circadian regulation of ion channels and their functions. *J.*  
7 *Neurochem.* 110, 1150-1169.

8 Ko, M.L., Liu, Y., Dryer, S.E., Ko, G.Y., 2007. The expression of L-type voltage-gated  
9 calcium channels in retinal photoreceptors is under circadian control. *J. Neurochem.* 103, 784-  
10 792.

11 Koenekoop, R.K., Loyer, M., Hand, C.K., Al Mahdi, H., Dembinska, O., Beneish, R., Racine,  
12 J., Rouleau, G.A., 2003. Novel RPGR mutations with distinct retinitis pigmentosa phenotypes  
13 in French-Canadian families. *Am. J. Ophthalmol.* 136, 678-687.

14 Koh, V., Tan, C., Nah, G., Zhao, P., Yang, A., Lin, S.T., Wong, T.Y., Saw, S.M., Chia, A.,  
15 2014. Correlation of structural and electrophysiological changes in the retina of young high  
16 myopes. *Ophthalmic Physiol. Opt.* 34, 658-666.

17 Koike, C., Obara, T., Uriu, Y., Numata, T., Sanuki, R., Miyata, K., Koyasu, T., Ueno, S.,  
18 Funabiki, K., Tani, A., Ueda, H., Kondo, M., Mori, Y., Tachibana, M., Furukawa, T., 2010.  
19 TRPM1 is a component of the retinal ON bipolar cell transduction channel in the mGluR6  
20 cascade. *Proc Natl Acad Sci U S A* 107, 332-337.

21 Kolb, H., Nelson, R., 1981. Amacrine cells of the cat retina. *Vision Res.* 21, 1625-1633.

22 Kondo, M., Das, G., Imai, R., Santana, E., Nakashita, T., Imawaka, M., Ueda, K., Ohtsuka,  
23 H., Sakai, K., Aihara, T., Kato, K., Sugimoto, M., Ueno, S., Nishizawa, Y., Aguirre, G.D.,  
24 Miyadera, K., 2015. A Naturally Occurring Canine Model of Autosomal Recessive  
25 Congenital Stationary Night Blindness. *PLoS ONE* 10, e0137072.

26 Kozuka, T., Chaya, T., Tamalu, F., Shimada, M., Fujimaki-Aoba, K., Kuwahara, R.,  
27 Watanabe, S.I., Furukawa, T., 2017. The TRPM1 Channel Is Required for Development of  
28 the Rod ON Bipolar Cell-AII Amacrine Cell Pathway in the Retinal Circuit. *J. Neurosci.* 37,  
29 9889-9900.

30 Lakkis, M.M., Bergenhem, N.C., O'Shea, K.S., Tashian, R.E., 1997. Expression of the  
31 acatalytic carbonic anhydrase VIII gene, Car8, during mouse embryonic development.  
32 *Histochem. J.* 29, 135-141.

33 Lam, C.S., Goldschmidt, E., Edwards, M.H., 2004. Prevalence of myopia in local and  
34 international schools in Hong Kong. *Optom. Vis. Sci.* 81, 317-322.

35 Lan, W., Feldkaemper, M., Schaeffel, F., 2014. Intermittent episodes of bright light suppress  
36 myopia in the chicken more than continuous bright light. *PLoS ONE* 9, e110906.

37 Landis, E.G., Chrenek, M.A., Chakraborty, R., Strickland, R., Bergen, M., Yang, V., Iuvone,  
38 P.M., Pardue, M.T., 2020. Increased endogenous dopamine prevents myopia in mice. *Exp.*  
39 *Eye Res.* 193, 107956.

- 1 Lawan, A., Torrance, E., Al-Harathi, S., Shweash, M., Alnasser, S., Neamatallah, T.,  
2 Schroeder, J., Plevin, R., 2012. MKP-2: out of the DUSP-bin and back into the limelight.  
3 *Biochem. Soc. Trans.* 40, 235-239.
- 4 Leamey, C.A., Protti, D.A., Dreher, B., 2008. Comparative survey of the mammalian visual  
5 system with reference to the mouse, in: Chalupa, L.M., Williams, R.W. (Eds.), *Eye, retina,*  
6 *and visual system of the mouse.* MIT Press, Cambridge, Massachusetts, pp. 35-60.
- 7 Lewallen, S., Lowdon, R., Courtright, P., Mehl, G.L., 1995. A population-based survey of the  
8 prevalence of refractive error in Malawi. *Ophthalmic Epidemiol.* 2, 145-149.
- 9 Li, J., Zhang, Q., 2017. Insight into the molecular genetics of myopia. *Mol. Vis.* 23, 1048-  
10 1080.
- 11 Li, Z., Sergouniotis, P.I., Michaelides, M., Mackay, D.S., Wright, G.A., Devery, S., Moore,  
12 A.T., Holder, G.E., Robson, A.G., Webster, A.R., 2009. Recessive mutations of the gene  
13 TRPM1 abrogate ON bipolar cell function and cause complete congenital stationary night  
14 blindness in humans. *Am. J. Hum. Genet.* 85, 711-719.
- 15 Lin, H.J., Wan, L., Tsai, Y., Liu, S.C., Chen, W.C., Tsai, S.W., Tsai, F.J., 2009. Sclera-related  
16 gene polymorphisms in high myopia. *Mol. Vis.* 15, 1655-1663.
- 17 Lin, L.L., Shih, Y.F., Hsiao, C.K., Chen, C.J., 2004. Prevalence of myopia in Taiwanese  
18 schoolchildren: 1983 to 2000. *Ann. Acad. Med. Singapore* 33, 27-33.
- 19 Lin, Y., Ding, Y., Jiang, D., Li, C., Huang, X., Liu, L., Xiao, H., Vasudevan, B., Chen, Y.,  
20 2020. Genome-Wide Association of Genetic Variants With Refraction, Axial Length, and  
21 Corneal Curvature: A Longitudinal Study of Chinese Schoolchildren. *Front Genet* 11, 276.
- 22 Lindquist, A.C., Cama, A., Keefte, J.E., 2011. Screening for uncorrected refractive error in  
23 secondary school-age students in Fiji. *Clin Exp Ophthalmol* 39, 330-335.
- 24 Lithander, J., 1999. Prevalence of myopia in school children in the Sultanate of Oman: a  
25 nation-wide study of 6292 randomly selected children. *Acta Ophthalmol. Scand.* 77, 306-309.
- 26 Liu, H.H., Xu, L., Wang, Y.X., Wang, S., You, Q.S., Jonas, J.B., 2010. Prevalence and  
27 progression of myopic retinopathy in Chinese adults: the Beijing Eye Study. *Ophthalmology*  
28 117, 1763-1768.
- 29 Liu, X., Shen, M., Yuan, Y., Huang, S., Zhu, D., Ma, Q., Ye, X., Lu, F., 2015. Macular  
30 Thickness Profiles of Intraretinal Layers in Myopia Evaluated by Ultrahigh-Resolution  
31 Optical Coherence Tomography. *Am. J. Ophthalmol.* 160, 53-61 e52.
- 32 Lopes, M.C., Andrew, T., Carbonaro, F., Spector, T.D., Hammond, C.J., 2009. Estimating  
33 heritability and shared environmental effects for refractive error in twin and family studies.  
34 *Invest Ophthalmol Vis Sci* 50, 126-131.
- 35 Lyhne, N., Sjolie, A.K., Kyvik, K.O., Green, A., 2001. The importance of genes and  
36 environment for ocular refraction and its determiners: a population based study among 20-45  
37 year old twins. *Br. J. Ophthalmol.* 85, 1470-1476.

1 Ma, M., Zhang, Z., Du, E., Zheng, W., Gu, Q., Xu, X., Ke, B., 2014. Wnt signaling in form  
2 deprivation myopia of the mice retina. *PLoS One* 9, e91086.

3 Macosko, E.Z., Basu, A., Satija, R., Nemesh, J., Shekhar, K., Goldman, M., Tirosh, I., Bialas,  
4 A.R., Kamitaki, N., Martersteck, E.M., Trombetta, J.J., Weitz, D.A., Sanes, J.R., Shalek,  
5 A.K., Regev, A., McCarroll, S.A., 2015. Highly Parallel Genome-wide Expression Profiling  
6 of Individual Cells Using Nanoliter Droplets. *Cell* 161, 1202-1214.

7 Maddox, D.M., Vessey, K.A., Yarbrough, G.L., Invergo, B.M., Cantrell, D.R., Inayat, S.,  
8 Balannik, V., Hicks, W.L., Hawes, N.L., Byers, S., Smith, R.S., Hurd, R., Howell, D., Gregg,  
9 R.G., Chang, B., Naggert, J.K., Troy, J.B., Pinto, L.H., Nishina, P.M., McCall, M.A., 2008.  
10 Allelic variance between GRM6 mutants, Grm6nob3 and Grm6nob4 results in differences in  
11 retinal ganglion cell visual responses. *J. Physiol.* 586, 4409-4424.

12 Manolakos, E., Kefalas, K., Vetro, A., Oikonomidou, E., Daskalakis, G., Psara, N., Siomou,  
13 E., Papageorgiou, E., Sevastopoulou, E., Konstantinidou, A., Vrachnis, N., Thomaidis, L.,  
14 Zuffardi, O., Papoulidis, I., 2013. Prenatal diagnosis of two de novo 4q35-qter deletions  
15 characterized by array-CGH. *Mol. Cytogenet.* 6, 47.

16 Mao, C.A., Kiyama, T., Pan, P., Furuta, Y., Hadjantonakis, A.K., Klein, W.H., 2008.  
17 Eomesodermin, a target gene of Pou4f2, is required for retinal ganglion cell and optic nerve  
18 development in the mouse. *Development* 135, 271-280.

19 Mao, J., Liu, S., Qin, W., Li, F., Wu, X., Tan, Q., 2010. Levodopa inhibits the development of  
20 form-deprivation myopia in guinea pigs. *Optom. Vis. Sci.* 87, 53-60.

21 Masu, M., Iwakabe, H., Tagawa, Y., Miyoshi, T., Yamashita, M., Fukuda, Y., Sasaki, H.,  
22 Hiroi, K., Nakamura, Y., Shigemoto, R., et al., 1995. Specific deficit of the ON response in  
23 visual transmission by targeted disruption of the mGluR6 gene. *Cell* 80, 757-765.

24 McBrien, N.A., Gentle, A., 2003. Role of the sclera in the development and pathological  
25 complications of myopia. *Prog. Retin. Eye Res.* 22, 307-338.

26 McCall, M.A., Lukasiewicz, P.D., Gregg, R.G., Peachey, N.S., 2002. Elimination of the rho1  
27 subunit abolishes GABA(C) receptor expression and alters visual processing in the mouse  
28 retina. *J. Neurosci.* 22, 4163-4174.

29 McGlinn, A.M., Baldwin, D.A., Tobias, J.W., Budak, M.T., Khurana, T.S., Stone, R.A., 2007.  
30 Form-deprivation myopia in chick induces limited changes in retinal gene expression. *Invest*  
31 *Ophthalmol Vis Sci* 48, 3430-3436.

32 Miyake, M., Yamashiro, K., Tabara, Y., Suda, K., Morooka, S., Nakanishi, H., Khor, C.C.,  
33 Chen, P., Qiao, F., Nakata, I., Akagi-Kurashige, Y., Gotoh, N., Tsujikawa, A., Meguro, A.,  
34 Kusuhara, S., Polasek, O., Hayward, C., Wright, A.F., Campbell, H., Richardson, A.J.,  
35 Schache, M., Takeuchi, M., Mackey, D.A., Hewitt, A.W., Cuellar, G., Shi, Y., Huang, L.,  
36 Yang, Z., Leung, K.H., Kao, P.Y., Yap, M.K., Yip, S.P., Moriyama, M., Ohno-Matsui, K.,  
37 Mizuki, N., MacGregor, S., Vitart, V., Aung, T., Saw, S.M., Tai, E.S., Wong, T.Y., Cheng,  
38 C.Y., Baird, P.N., Yamada, R., Matsuda, F., Nagahama Study, G., Yoshimura, N., 2015.  
39 Identification of myopia-associated WNT7B polymorphisms provides insights into the  
40 mechanism underlying the development of myopia. *Nature communications* 6, 6689.

- 1 Miyake, Y., Yagasaki, K., Horiguchi, M., Kawase, Y., Kanda, T., 1986. Congenital stationary  
2 night blindness with negative electroretinogram. A new classification. Arch. Ophthalmol. 104,  
3 1013-1020.
- 4 Morgan, I., Rose, K., 2005. How genetic is school myopia? Prog. Retin. Eye Res. 24, 1-38.
- 5 Morgan, I.G., 2003. The biological basis of myopic refractive error. Clin Exp Optom 86, 276-  
6 288.
- 7 Morgan, I.G., French, A.N., Ashby, R.S., Guo, X., Ding, X., He, M., Rose, K.A., 2018. The  
8 epidemics of myopia: Aetiology and prevention. Prog. Retin. Eye Res. 62, 134-149.
- 9 Morgan, I.G., Ohno-Matsui, K., Saw, S.M., 2012. Myopia. Lancet 379, 1739-1748.
- 10 Morgans, C.W., Zhang, J., Jeffrey, B.G., Nelson, S.M., Burke, N.S., Duvoisin, R.M., Brown,  
11 R.L., 2009. TRPM1 is required for the depolarizing light response in retinal ON-bipolar cells.  
12 Proc Natl Acad Sci U S A 106, 19174-19178.
- 13 Morris, B.J., Simpson, C.S., Mundell, S., Maceachern, K., Johnston, H.M., Nolan, A.M.,  
14 1997. Dynamic changes in NADPH-diaphorase staining reflect activity of nitric oxide  
15 synthase: evidence for a dopaminergic regulation of striatal nitric oxide release.  
16 Neuropharmacology 36, 1589-1599.
- 17 Musolf, A.M., Simpson, C.L., Moiz, B.A., Long, K.A., Portas, L., Murgia, F., Ciner, E.B.,  
18 Stambolian, D., Bailey-Wilson, J.E., 2017. Caucasian Families Exhibit Significant Linkage of  
19 Myopia to Chromosome 11p. Invest Ophthalmol Vis Sci 58, 3547-3554.
- 20 Nakamichi, Y., Shukunami, C., Yamada, T., Aihara, K., Kawano, H., Sato, T., Nishizaki, Y.,  
21 Yamamoto, Y., Shindo, M., Yoshimura, K., Nakamura, T., Takahashi, N., Kawaguchi, H.,  
22 Hiraki, Y., Kato, S., 2003. Chondromodulin I is a bone remodeling factor. Mol. Cell. Biol. 23,  
23 636-644.
- 24 Neitz, M., Neitz, J., 2021. Intermixing the OPN1LW and OPN1MW Genes Disrupts the  
25 Exonic Splicing Code Causing an Array of Vision Disorders. Genes (Basel) 12.
- 26 Neuille, M., El Shamieh, S., Orhan, E., Michiels, C., Antonio, A., Lancelot, M.E., Condroyer,  
27 C., Bujakowska, K., Poch, O., Sahel, J.A., Audo, I., Zeitz, C., 2014. Lrit3 deficient mouse  
28 (nob6): a novel model of complete congenital stationary night blindness (cCSNB). PLoS ONE  
29 9, e90342.
- 30 Neuille, M., Morgans, C.W., Cao, Y., Orhan, E., Michiels, C., Sahel, J.A., Audo, I., Duvoisin,  
31 R.M., Martemyanov, K.A., Zeitz, C., 2015. LRIT3 is essential to localize TRPM1 to the  
32 dendritic tips of depolarizing bipolar cells and may play a role in cone synapse formation.  
33 Eur. J. Neurosci. 42, 1966-1975.
- 34 Nguyen-Legros, J., Versaux-Botteri, C., Vernier, P., 1999. Dopamine receptor localization in  
35 the mammalian retina. Mol. Neurobiol. 19, 181-204.
- 36 Nishizaki, R., Ota, M., Inoko, H., Meguro, A., Shiota, T., Okada, E., Mok, J., Oka, A., Ohno,  
37 S., Mizuki, N., 2009. New susceptibility locus for high myopia is linked to the uromodulin-  
38 like 1 (UMODL1) gene region on chromosome 21q22.3. Eye (Lond) 23, 222-229.

- 1 Norton, T.T., McBrien, N.A., 1992. Normal development of refractive state and ocular  
2 component dimensions in the tree shrew (*Tupaia belangeri*). *Vision Res* 32, 833-842.
- 3 Ohlsson, L., 1963. Congenital Renal Disease, Deafness and Myopia in One Family. *Acta*  
4 *Med. Scand.* 174, 77-84.
- 5 Ohno-Matsui, K., Jonas, J.B., 2019. Posterior staphyloma in pathologic myopia. *Prog. Retin.*  
6 *Eye Res.* 70, 99-109.
- 7 Ohno-Matsui, K., Lai, T.Y., Lai, C.C., Cheung, C.M., 2016. Updates of pathologic myopia.  
8 *Prog. Retin. Eye Res.* 52, 156-187.
- 9 Orhan, E., Neuille, M., de Sousa Dias, M., Pugliese, T., Michiels, C., Condroyer, C., Antonio,  
10 A., Sahel, J.A., Audo, I., Zeitz, C., 2021. A New Mouse Model for Complete Congenital  
11 Stationary Night Blindness Due to Gpr179 Deficiency. *Int. J. Mol. Sci.* 22.
- 12 Orlandi, C., Posokhova, E., Masuho, I., Ray, T.A., Hasan, N., Gregg, R.G., Martemyanov,  
13 K.A., 2012. GPR158/179 regulate G protein signaling by controlling localization and activity  
14 of the RGS7 complexes. *J. Cell Biol.* 197, 711-719.
- 15 Ouyang, X.L., Chen, B.Y., Xie, Y.F., Wu, Y.D., Guo, S.J., Dong, X.Y., Wang, G.H., 2020.  
16 Whole transcriptome analysis on blue light-induced eye damage. *Int J Ophthalmol* 13, 1210-  
17 1222.
- 18 Pan, C.W., Ramamurthy, D., Saw, S.M., 2012. Worldwide prevalence and risk factors for  
19 myopia. *Ophthalmic Physiol. Opt.* 32, 3-16.
- 20 Pardue, M.T., Faulkner, A.E., Fernandes, A., Yin, H., Schaeffel, F., Williams, R.W.,  
21 Pozdeyev, N., Iuvone, P.M., 2008. High susceptibility to experimental myopia in a mouse  
22 model with a retinal on pathway defect. *Invest Ophthalmol Vis Sci* 49, 706-712.
- 23 Pardue, M.T., McCall, M.A., LaVail, M.M., Gregg, R.G., Peachey, N.S., 1998. A naturally  
24 occurring mouse model of X-linked congenital stationary night blindness. *Invest Ophthalmol*  
25 *Vis Sci* 39, 2443-2449.
- 26 Pardue, M.T., Peachey, N.S., 2014. Mouse b-wave mutants. *Doc. Ophthalmol.* 128, 77-89.
- 27 Pardue, M.T., Stone, R.A., Iuvone, P.M., 2013. Investigating mechanisms of myopia in mice.  
28 *Exp. Eye Res.* 114, 96-105.
- 29 Park, H., Tan, C.C., Faulkner, A., Jabbar, S.B., Schmid, G., Abey, J., Iuvone, P.M., Pardue,  
30 M.T., 2013. Retinal degeneration increases susceptibility to myopia in mice. *Mol. Vis.* 19,  
31 2068-2079.
- 32 Patterson, K.I., Brummer, T., O'Brien, P.M., Daly, R.J., 2009. Dual-specificity phosphatases:  
33 critical regulators with diverse cellular targets. *Biochem. J.* 418, 475-489.
- 34 Peachey, N.S., Ray, T.A., Florijn, R., Rowe, L.B., Sjoerdsma, T., Contreras-Alcantara, S.,  
35 Baba, K., Tosini, G., Pozdeyev, N., Iuvone, P.M., Bojang, P., Jr., Pearing, J.N., Simonsz,  
36 H.J., van Genderen, M., Birch, D.G., Traboulsi, E.I., Dorfman, A., Lopez, I., Ren, H.,  
37 Goldberg, A.F., Nishina, P.M., Lachapelle, P., McCall, M.A., Koenekoop, R.K., Bergen,  
38 A.A., Kamermans, M., Gregg, R.G., 2012. GPR179 is required for depolarizing bipolar cell

1 function and is mutated in autosomal-recessive complete congenital stationary night  
2 blindness. *Am. J. Hum. Genet.* 90, 331-339.

3 Pearing, J.N., Bojang, P., Jr., Shen, Y., Koike, C., Furukawa, T., Nawy, S., Gregg, R.G.,  
4 2011. A role for nyctalopin, a small leucine-rich repeat protein, in localizing the TRP  
5 melastatin 1 channel to retinal depolarizing bipolar cell dendrites. *J. Neurosci.* 31, 10060-  
6 10066.

7 Peet, J.A., Cotch, M.F., Wojciechowski, R., Bailey-Wilson, J.E., Stambolian, D., 2007.  
8 Heritability and familial aggregation of refractive error in the Old Order Amish. *Invest*  
9 *Ophthalmol Vis Sci* 48, 4002-4006.

10 Pemberton, J.W., Freeman, H.M., Schepens, C.L., 1966. Familial retinal detachment and the  
11 Ehlers-Danlos syndrome. *Arch. Ophthalmol.* 76, 817-824.

12 Perez-Roustit, S., Nguyen, D.T., Xerri, O., Robert, M.P., De Vergnes, N., Mincheva, Z.,  
13 Benistan, K., Bremond-Gignac, D., 2019. [Ocular manifestations in Ehlers-Danlos  
14 Syndromes: Clinical study of 21 patients]. *J. Fr. Ophtalmol.* 42, 722-729.

15 Petersen, H.H., Hilpert, J., Militz, D., Zandler, V., Jacobsen, C., Roebroek, A.J., Willnow,  
16 T.E., 2003. Functional interaction of megalin with the megalinbinding protein (MegBP), a  
17 novel tetratrico peptide repeat-containing adaptor molecule. *J. Cell Sci.* 116, 453-461.

18 Petry, H.M., Fox, R., Casagrande, V.A., 1984. Spatial contrast sensitivity of the tree shrew.  
19 *Vision Res* 24, 1037-1042.

20 Pinto, L.H., Vitaterna, M.H., Shimomura, K., Siepka, S.M., Balannik, V., McDearmon, E.L.,  
21 Omura, C., Lumayag, S., Invergo, B.M., Glawe, B., Cantrell, D.R., Inayat, S., Olvera, M.A.,  
22 Vessey, K.A., McCall, M.A., Maddox, D., Morgans, C.W., Young, B., Pletcher, M.T.,  
23 Mullins, R.F., Troy, J.B., Takahashi, J.S., 2007. Generation, identification and functional  
24 characterization of the nob4 mutation of *Grm6* in the mouse. *Vis. Neurosci.* 24, 111-123.

25 Pittendrigh, C.S., 1993. Temporal organization: reflections of a Darwinian clock-watcher.  
26 *Annu. Rev. Physiol.* 55, 16-54.

27 Plossl, K., Weber, B.H., Friedrich, U., 2017. The X-linked juvenile retinoschisis protein  
28 retinoschisin is a novel regulator of mitogen-activated protein kinase signalling and apoptosis  
29 in the retina. *J. Cell. Mol. Med.* 21, 768-780.

30 Podkolodnaya, O.A., Yarkova, E.E., Demenkov, P.S., Konovalova, O.S., Kolchanov, N.A.,  
31 2011. Application of the ANDCell Computer System to Reconstruction and Analysis of  
32 Associative Networks Describing Potential Relationships between Myopia and Glaucoma.  
33 *Russian Journal of Genetics: Applied Research* 1, 21.

34 Pokharel, G.P., Negrel, A.D., Munoz, S.R., Ellwein, L.B., 2000. Refractive Error Study in  
35 Children: results from Mechi Zone, Nepal. *Am. J. Ophthalmol.* 129, 436-444.

36 Prasanna, G., Narayan, S., Krishnamoorthy, R.R., Yorio, T., 2003. Eyeing endothelins: a  
37 cellular perspective. *Mol. Cell. Biochem.* 253, 71-88.

38 Prusky, G.T., Douglas, R.M., 2004. Characterization of mouse cortical spatial vision. *Vision*  
39 *Res.* 44, 3411-3418.

1 Pusch, C.M., Zeitz, C., Brandau, O., Pesch, K., Achatz, H., Feil, S., Scharfe, C., Maurer, J.,  
2 Jacobi, F.K., Pinckers, A., Andreasson, S., Hardcastle, A., Wissinger, B., Berger, W., Meindl,  
3 A., 2000. The complete form of X-linked congenital stationary night blindness is caused by  
4 mutations in a gene encoding a leucine-rich repeat protein. *Nat. Genet.* 26, 324-327.

5 Puthussery, T., Gayet-Primo, J., Taylor, W.R., 2011. Carbonic anhydrase-related protein VIII  
6 is expressed in rod bipolar cells and alters signaling at the rod bipolar to AII-amacrine cell  
7 synapse in the mammalian retina. *Eur. J. Neurosci.* 34, 1419-1431.

8 Pyeritz, R.E., McKusick, V.A., 1979. The Marfan syndrome: diagnosis and management. *N.*  
9 *Engl. J. Med.* 300, 772-777.

10 Qian, H., Ji, R., Gregg, R.G., Peachey, N.S., 2015. Identification of a new mutant allele,  
11 *Grm6(nob7)*, for complete congenital stationary night blindness. *Vis. Neurosci.* 32, E004.

12 Qiao-Grider, Y., Hung, L.F., Kee, C.S., Ramamirtham, R., Smith, E.L., 3rd, 2007. Normal  
13 ocular development in young rhesus monkeys (*Macaca mulatta*). *Vision Res* 47, 1424-1444.

14 Quinn, K.E., Mackie, D.I., Caron, K.M., 2018. Emerging roles of atypical chemokine receptor  
15 3 (ACKR3) in normal development and physiology. *Cytokine* 109, 17-23.

16 Rattner, A., Nathans, J., 2005. The genomic response to retinal disease and injury: evidence  
17 for endothelin signaling from photoreceptors to glia. *J. Neurosci.* 25, 4540-4549.

18 Riddell, N., Crewther, S.G., 2017. Novel evidence for complement system activation in chick  
19 myopia and hyperopia models: a meta-analysis of transcriptome datasets. *Sci Rep* 7, 9719.

20 Riddell, N., Giummarra, L., Hall, N.E., Crewther, S.G., 2016. Bidirectional Expression of  
21 Metabolic, Structural, and Immune Pathways in Early Myopia and Hyperopia. *Front.*  
22 *Neurosci.* 10, 390.

23 Rose, K.A., Morgan, I.G., Ip, J., Kifley, A., Huynh, S., Smith, W., Mitchell, P., 2008.  
24 Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology* 115, 1279-  
25 1285.

26 Rossi, M.R., DiMaio, M.S., Xiang, B., Lu, K., Kaymakcalan, H., Seashore, M., Mahoney,  
27 M.J., Li, P., 2009. Clinical and genomic characterization of distal duplications and deletions  
28 of chromosome 4q: study of two cases and review of the literature. *Am. J. Med. Genet. A.*  
29 149A, 2788-2794.

30 Roth, S., Shaikh, A.R., Hennelly, M.M., Li, Q., Bindokas, V., Graham, C.E., 2003. Mitogen-  
31 activated protein kinases and retinal ischemia. *Invest Ophthalmol Vis Sci* 44, 5383-5395.

32 Rouillard, A.D., Gundersen, G.W., Fernandez, N.F., Wang, Z., Monteiro, C.D., McDermott,  
33 M.G., Ma'ayan, A., 2016. The harmonizome: a collection of processed datasets gathered to  
34 serve and mine knowledge about genes and proteins. *Database (Oxford)* 2016.

35 Rozzo, A., Ballerini, L., Nistri, A., 1999. Antagonism by (1,2,5,6-tetrahydropyridine-4-yl)  
36 methylphosphinic acid of synaptic transmission in the neonatal rat spinal cord in vitro: an  
37 electrophysiological study. *Neuroscience* 90, 1085-1092.



1 Salazar, N., Munoz, D., Kallifatidis, G., Singh, R.K., Jorda, M., Lokeshwar, B.L., 2014. The  
2 chemokine receptor CXCR7 interacts with EGFR to promote breast cancer cell proliferation.  
3 *Mol. Cancer* 13, 198.

4 Sanchez Tocino, H., Diez Montero, C., Villanueva Gomez, A., Lobo Valentin, R., Montero-  
5 Moreno, J.A., 2019. Phenotypic high myopia in X-linked retinitis pigmentosa secondary to a  
6 novel mutation in the RPGR gene. *Ophthalmic Genet.* 40, 170-176.

7 Sanford, L.P., Ormsby, I., Gittenberger-de Groot, A.C., Sariola, H., Friedman, R., Boivin,  
8 G.P., Cardell, E.L., Doetschman, T., 1997. TGFbeta2 knockout mice have multiple  
9 developmental defects that are non-overlapping with other TGFbeta knockout phenotypes.  
10 *Development* 124, 2659-2670.

11 Scalabrino, M.L., Boye, S.L., Fransen, K.M., Noel, J.M., Dyka, F.M., Min, S.H., Ruan, Q.,  
12 De Leeuw, C.N., Simpson, E.M., Gregg, R.G., McCall, M.A., Peachey, N.S., Boye, S.E.,  
13 2015. Intravitreal delivery of a novel AAV vector targets ON bipolar cells and restores visual  
14 function in a mouse model of complete congenital stationary night blindness. *Hum. Mol.*  
15 *Genet.* 24, 6229-6239.

16 Schache, M., Chen, C.Y., Pertile, K.K., Richardson, A.J., Dirani, M., Mitchell, P., Baird,  
17 P.N., 2009. Fine mapping linkage analysis identifies a novel susceptibility locus for myopia  
18 on chromosome 2q37 adjacent to but not overlapping MYP12. *Mol. Vis.* 15, 722-730.

19 Schaeffel, F., Burkhardt, E., Howland, H.C., Williams, R.W., 2004. Measurement of  
20 refractive state and deprivation myopia in two strains of mice. *Optom. Vis. Sci.* 81, 99-110.

21 Schaeffel, F., Feldkaemper, M., 2015. Animal models in myopia research. *Clin Exp Optom*  
22 98, 507-517.

23 Schatz, A., Kelbsch, C., Zeitz, C., Kohl, S., Zrenner, E., Gekeler, F., Wilhelm, H., Wilhelm,  
24 B., Willmann, G., 2019. Disinhibition of intrinsic photosensitive retinal ganglion cells in  
25 patients with X-linked congenital stationary night blindness. *Graefes Arch Clin Exp*  
26 *Ophthalmol* 257, 1207-1215.

27 Schippert, R., Burkhardt, E., Feldkaemper, M., Schaeffel, F., 2007. Relative axial myopia in  
28 *Egr-1* (ZENK) knockout mice. *Invest Ophthalmol Vis Sci* 48, 11-17.

29 Schippert, R., Schaeffel, F., Feldkaemper, M.P., 2008. Microarray analysis of retinal gene  
30 expression in chicks during imposed myopic defocus. *Mol. Vis.* 14, 1589-1599.

31 Schmid, K.L., Strasberg, G., Rayner, C.L., Hartfield, P.J., 2013. The effects and interactions  
32 of GABAergic and dopaminergic agents in the prevention of form deprivation myopia by  
33 brief periods of normal vision. *Exp. Eye Res.* 110, 88-95.

34 Schmid, K.L., Wildsoet, C.F., 1998. Assessment of visual acuity and contrast sensitivity in  
35 the chick using an optokinetic nystagmus paradigm. *Vision Res* 38, 2629-2634.

36 Seternes, O.M., Kidger, A.M., Keyse, S.M., 2019. Dual-specificity MAP kinase phosphatases  
37 in health and disease. *Biochim Biophys Acta Mol Cell Res* 1866, 124-143.

1 She, M., Li, B., Li, T., Hu, Q., Zhou, X., 2021. Modulation of the ERK1/2-MMP-2 pathway  
2 in the sclera of guinea pigs following induction of myopia by flickering light. *Exp Ther Med*  
3 21, 371.

4 Shekhar, K., Lapan, S.W., Whitney, I.E., Tran, N.M., Macosko, E.Z., Kowalczyk, M.,  
5 Adiconis, X., Levin, J.Z., Nemesh, J., Goldman, M., McCarroll, S.A., Cepko, C.L., Regev,  
6 A., Sanes, J.R., 2016. Comprehensive Classification of Retinal Bipolar Neurons by Single-  
7 Cell Transcriptomics. *Cell* 166, 1308-1323 e1330.

8 Shelton, L., Troilo, D., Lerner, M.R., Gusev, Y., Brackett, D.J., Rada, J.S., 2008. Microarray  
9 analysis of choroid/RPE gene expression in marmoset eyes undergoing changes in ocular  
10 growth and refraction. *Mol. Vis.* 14, 1465-1479.

11 Shen, W., Sivak, J.G., 2007. Eyes of a lower vertebrate are susceptible to the visual  
12 environment. *Invest Ophthalmol Vis Sci* 48, 4829-4837.

13 Shibuya, K., Nagamine, K., Okui, M., Ohsawa, Y., Asakawa, S., Minoshima, S., Hase, T.,  
14 Kudoh, J., Shimizu, N., 2004. Initial characterization of an uromodulin-like 1 gene on human  
15 chromosome 21q22.3. *Biochem. Biophys. Res. Commun.* 319, 1181-1189.

16 Shukunami, C., Yamamoto, S., Tanabe, T., Hiraki, Y., 1999. Generation of multiple  
17 transcripts from the chicken chondromodulin-I gene and their expression during embryonic  
18 development. *FEBS Lett.* 456, 165-170.

19 Siegert, S., Cabuy, E., Scherf, B.G., Kohler, H., Panda, S., Le, Y.Z., Fehling, H.J., Gaidatzis,  
20 D., Stadler, M.B., Roska, B., 2012. Transcriptional code and disease map for adult retinal cell  
21 types. *Nat. Neurosci.*

22 Siegert, S., Scherf, B.G., Del Punta, K., Didkovsky, N., Heintz, N., Roska, B., 2009. Genetic  
23 address book for retinal cell types. *Nat. Neurosci.* 12, 1197-1204.

24 Siegwart, J.T., Jr., Norton, T.T., 2002. The time course of changes in mRNA levels in tree  
25 shrew sclera during induced myopia and recovery. *Invest Ophthalmol Vis Sci* 43, 2067-2075.

26 Smith, E.L., 3rd, Hung, L.F., Huang, J., 2012. Protective effects of high ambient lighting on  
27 the development of form-deprivation myopia in rhesus monkeys. *Invest Ophthalmol Vis Sci*  
28 53, 421-428.

29 Song, Y., Zhang, F., Zhao, Y., Sun, M., Tao, J., Liang, Y., Ma, L., Yu, Y., Wang, J., Hao, J.,  
30 2016. Enlargement of the Axial Length and Altered Ultrastructural Features of the Sclera in a  
31 Mutant Lumican Transgenic Mouse Model. *PLoS ONE* 11, e0163165.

32 Specht, D., Wu, S.B., Turner, P., Dearden, P., Koentgen, F., Wolfrum, U., Maw, M.,  
33 Brandstatter, J.H., tom Dieck, S., 2009. Effects of presynaptic mutations on a postsynaptic  
34 Cacna1s calcium channel colocalized with mGluR6 at mouse photoreceptor ribbon synapses.  
35 *Invest Ophthalmol Vis Sci* 50, 505-515.

36 Spencer, H.L., Jover, E., Cathery, W., Avolio, E., Rodriguez-Arabaolaza, I., Thomas, A.C.,  
37 Alvino, V.V., Sala-Newby, G., Dang, Z., Fagnano, M., Reni, C., Rowlinson, J., Vono, R.,  
38 Spinetti, G., Beltrami, A.P., Gargioli, C., Caporali, A., Angelini, G., Madeddu, P., 2019. Role  
39 of TPBG (Trophoblast Glycoprotein) Antigen in Human Pericyte Migratory and Angiogenic  
40 Activity. *Arterioscler. Thromb. Vasc. Biol.* 39, 1113-1124.

1 Stoimenova, B.D., 2007. The effect of myopia on contrast thresholds. *Invest Ophthalmol Vis*  
2 *Sci* 48, 2371-2374.

3 Stone, R.A., Lin, T., Laties, A.M., Iuvone, P.M., 1989. Retinal dopamine and form-  
4 deprivation myopia. *Proc Natl Acad Sci U S A* 86, 704-706.

5 Stone, R.A., Liu, J., Sugimoto, R., Capehart, C., Zhu, X., Pendrak, K., 2003. GABA,  
6 experimental myopia, and ocular growth in chick. *Invest Ophthalmol Vis Sci* 44, 3933-3946.

7 Stone, R.A., McGlinn, A.M., Baldwin, D.A., Tobias, J.W., Iuvone, P.M., Khurana, T.S.,  
8 2011. Image defocus and altered retinal gene expression in chick: clues to the pathogenesis of  
9 ametropia. *Invest Ophthalmol Vis Sci* 52, 5765-5777.

10 Stora, S., Conte, M., Chouery, E., Richa, S., Jalkh, N., Gillart, A.C., Joannis, A.L.,  
11 Megarbane, A., 2009. A 56-year-old female patient with facio-oculo-acoustico-renal  
12 syndrome (FOAR) syndrome. Report on the natural history and of a novel mutation. *Eur. J.*  
13 *Med. Genet.* 52, 341-343.

14 Storm, T., Heegaard, S., Christensen, E.I., Nielsen, R., 2014. Megalin-deficiency causes high  
15 myopia, retinal pigment epithelium-macromelanosomes and abnormal development of the  
16 ciliary body in mice. *Cell Tissue Res.* 358, 99-107.

17 Strom, T.M., Nyakatura, G., Apfelstedt-Sylla, E., Hellebrand, H., Lorenz, B., Weber, B.H.,  
18 Wutz, K., Gutwillinger, N., Ruther, K., Drescher, B., Sauer, C., Zrenner, E., Meitinger, T.,  
19 Rosenthal, A., Meindl, A., 1998. An L-type calcium-channel gene mutated in incomplete X-  
20 linked congenital stationary night blindness. *Nat. Genet.* 19, 260-263.

21 Summers, J.A., Schaeffel, F., Marcos, S., Wu, H., Tkatchenko, A.V., 2021. Functional  
22 integration of eye tissues and refractive eye development: Mechanisms and pathways. *Exp*  
23 *Eye Res*, 108693.

24 Suzuki, A., Yanagisawa, M., Greene, R.W., 2020. Loss of Arc attenuates the behavioral and  
25 molecular responses for sleep homeostasis in mice. *Proc Natl Acad Sci U S A* 117, 10547-  
26 10553.

27 Sweeney, N.T., Tierney, H., Feldheim, D.A., 2014. Tbr2 is required to generate a neural  
28 circuit mediating the pupillary light reflex. *J. Neurosci.* 34, 5447-5453.

29 Takeuchi, H., Horie, S., Moritoh, S., Matsushima, H., Hori, T., Kimori, Y., Kitano, K., Tsubo,  
30 Y., Tachibana, M., Koike, C., 2018. Different Activity Patterns in Retinal Ganglion Cells of  
31 TRPM1 and mGluR6 Knockout Mice. *Biomed Res Int* 2018, 2963232.

32 Tarpey, P., Thomas, S., Sarvananthan, N., Mallya, U., Lisgo, S., Talbot, C.J., Roberts, E.O.,  
33 Awan, M., Surendran, M., McLean, R.J., Reinecke, R.D., Langmann, A., Lindner, S., Koch,  
34 M., Jain, S., Woodruff, G., Gale, R.P., Degg, C., Drouzas, K., Asproudis, I., Zubcov, A.A.,  
35 Pieh, C., Veal, C.D., Machado, R.D., Backhouse, O.C., Baumber, L., Constantinescu, C.S.,  
36 Brodsky, M.C., Hunter, D.G., Hertle, R.W., Read, R.J., Edkins, S., O'Meara, S., Parker, A.,  
37 Stevens, C., Teague, J., Wooster, R., Futreal, P.A., Trembath, R.C., Stratton, M.R., Raymond,  
38 F.L., Gottlob, I., 2006. Mutations in FRMD7, a newly identified member of the FERM  
39 family, cause X-linked idiopathic congenital nystagmus. *Nat. Genet.* 38, 1242-1244.

1 Tedja, M.S., Haarman, A.E.G., Meester-Smoor, M.A., Kaprio, J., Mackey, D.A.,  
2 Guggenheim, J.A., Hammond, C.J., Verhoeven, V.J.M., Klaver, C.C.W., Consortium, C.,  
3 2019. IMI - Myopia Genetics Report. *Invest Ophthalmol Vis Sci* 60, M89-M105.

4 Tedja, M.S., Wojciechowski, R., Hysi, P.G., Eriksson, N., Furlotte, N.A., Verhoeven, V.J.M.,  
5 Iglesias, A.I., Meester-Smoor, M.A., Thompson, S.W., Fan, Q., Khawaja, A.P., Cheng, C.Y.,  
6 Hohn, R., Yamashiro, K., Wenocur, A., Grazal, C., Haller, T., Metspalu, A., Wedenoja, J.,  
7 Jonas, J.B., Wang, Y.X., Xie, J., Mitchell, P., Foster, P.J., Klein, B.E.K., Klein, R., Paterson,  
8 A.D., Hosseini, S.M., Shah, R.L., Williams, C., Teo, Y.Y., Tham, Y.C., Gupta, P., Zhao, W.,  
9 Shi, Y., Saw, W.Y., Tai, E.S., Sim, X.L., Huffman, J.E., Polasek, O., Hayward, C., Bencic,  
10 G., Rudan, I., Wilson, J.F., Consortium, C., andMe Research, T., Eye, U.K.B., Vision, C.,  
11 Joshi, P.K., Tsujikawa, A., Matsuda, F., Whisenhunt, K.N., Zeller, T., van der Spek, P.J.,  
12 Haak, R., Meijers-Heijboer, H., van Leeuwen, E.M., Iyengar, S.K., Lass, J.H., Hofman, A.,  
13 Rivadeneira, F., Uitterlinden, A.G., Vingerling, J.R., Lehtimäki, T., Raitakari, O.T., Biino, G.,  
14 Concas, M.P., Schwantes-An, T.H., Igo, R.P., Jr., Cuellar-Partida, G., Martin, N.G., Craig,  
15 J.E., Gharahkhani, P., Williams, K.M., Nag, A., Rahi, J.S., Cumberland, P.M., Delcourt, C.,  
16 Bellenguez, C., Ried, J.S., Bergen, A.A., Meitinger, T., Gieger, C., Wong, T.Y., Hewitt,  
17 A.W., Mackey, D.A., Simpson, C.L., Pfeiffer, N., Parssinen, O., Baird, P.N., Vitart, V., Amin,  
18 N., van Duijn, C.M., Bailey-Wilson, J.E., Young, T.L., Saw, S.M., Stambolian, D.,  
19 MacGregor, S., Guggenheim, J.A., Tung, J.Y., Hammond, C.J., Klaver, C.C.W., 2018.  
20 Genome-wide association meta-analysis highlights light-induced signaling as a driver for  
21 refractive error. *Nat. Genet.* 50, 834-848.

22 Teikari, J.M., Kaprio, J., Koskenvuo, M.K., Vannas, A., 1988. Heritability estimate for  
23 refractive errors--a population-based sample of adult twins. *Genet. Epidemiol.* 5, 171-181.

24 Tejedor, J., de la Villa, P., 2003a. Refractive changes induced by form deprivation in the  
25 mouse eye. *Investigative Ophthalmology & Visual Science* 44, 32-36.

26 Tejedor, J., de la Villa, P., 2003b. Refractive changes induced by form deprivation in the  
27 mouse eye. *Invest Ophthalmol Vis Sci* 44, 32-36.

28 Tekin, M., Chioza, B.A., Matsumoto, Y., Diaz-Horta, O., Cross, H.E., Duman, D., Kokotas,  
29 H., Moore-Barton, H.L., Sakoori, K., Ota, M., Odaka, Y.S., Foster, J., 2nd, Cengiz, F.B.,  
30 Tokgoz-Yilmaz, S., Tekeli, O., Grigoriadou, M., Petersen, M.B., Sreekantan-Nair, A., Gurtz,  
31 K., Xia, X.J., Pandya, A., Patton, M.A., Young, J.I., Aruga, J., Crosby, A.H., 2013. SLITRK6  
32 mutations cause myopia and deafness in humans and mice. *J Clin Invest* 123, 2094-2102.

33 Thomson, K., Karouta, C., Morgan, I., Kelly, T., Ashby, R., 2019. Effectiveness and safety of  
34 topical levodopa in a chick model of myopia. *Sci Rep* 9, 18345.

35 Tkatchenko, A.V., Luo, X., Tkatchenko, T.V., Vaz, C., Tanavde, V.M., Maurer-Stroh, S.,  
36 Zauscher, S., Gonzalez, P., Young, T.L., 2016. Large-Scale microRNA Expression Profiling  
37 Identifies Putative Retinal miRNA-mRNA Signaling Pathways Underlying Form-Deprivation  
38 Myopia in Mice. *PLoS ONE* 11, e0162541.

39 Tkatchenko, A.V., Shen, Y., Tkatchenko, T.V., 2012. Genetic background modulates  
40 refractive eye development and susceptibility to myopia in the mouse. *Invest Ophthalmol Vis*  
41 *Sci* 53, E-Abstract 3465.

1 Tkatchenko, A.V., Tkatchenko, T.V., Guggenheim, J.A., Verhoeven, V.J., Hysi, P.G.,  
2 Wojciechowski, R., Singh, P.K., Kumar, A., Thinakaran, G., Consortium for Refractive, E.,  
3 Myopia, Williams, C., 2015. APLP2 Regulates Refractive Error and Myopia Development in  
4 Mice and Humans. *PLoS Genet* 11, e1005432.

5 Tkatchenko, A.V., Walsh, P.A., Tkatchenko, T.V., Gustincich, S., Raviola, E., 2006. Form  
6 deprivation modulates retinal neurogenesis in primate experimental myopia. *Proc Natl Acad*  
7 *Sci U S A* 103, 4681-4686.

8 Tkatchenko, T.V., Shah, R.L., Nagasaki, T., Tkatchenko, A.V., 2019. Analysis of genetic  
9 networks regulating refractive eye development in collaborative cross progenitor strain mice  
10 reveals new genes and pathways underlying human myopia. *BMC Med. Genomics* 12, 113.

11 Tkatchenko, T.V., Shen, Y., Braun, R.D., Bawa, G., Kumar, P., Avrutsky, I., Tkatchenko,  
12 A.V., 2013. Photopic visual input is necessary for emmetropization in mice. *Exp Eye Res*  
13 115C, 87-95.

14 Tkatchenko, T.V., Shen, Y., Tkatchenko, A.V., 2010. Mouse experimental myopia has  
15 features of primate myopia. *Invest Ophthalmol Vis Sci* 51, 1297-1303.

16 Tkatchenko, T.V., Tkatchenko, A.V., 2019. Pharmacogenomic approach to antimyopia drug  
17 development: pathways lead the way. *Trends Pharmacol Sci* 40, 834-853.

18 Tkatchenko, T.V., Tkatchenko, A.V., 2021a. Genetic network regulating visual acuity makes  
19 limited contribution to visually guided eye emmetropization. *Genomics* 113, 2780-2792.

20 Tkatchenko, T.V., Tkatchenko, A.V., 2021b. Genome-wide analysis of retinal transcriptome  
21 reveals common genetic network underlying perception of contrast and optical defocus  
22 detection. *BMC Med. Genomics* 14, 153.

23 Tkatchenko, T.V., Troilo, D., Benavente-Perez, A., Tkatchenko, A.V., 2018. Gene expression  
24 in response to optical defocus of opposite signs reveals bidirectional mechanism of visually  
25 guided eye growth. *PLoS Biol.* 16, e2006021.

26 Tran-Viet, K.N., Powell, C., Barathi, V.A., Klemm, T., Maurer-Stroh, S., Limviphuvadh, V.,  
27 Soler, V., Ho, C., Yanovitch, T., Schneider, G., Li, Y.J., Nading, E., Metlapally, R., Saw,  
28 S.M., Goh, L., Rozen, S., Young, T.L., 2013. Mutations in SCO2 are associated with  
29 autosomal-dominant high-grade myopia. *Am J Hum Genet* 92, 820-826.

30 Troilo, D., Smith, E.L., 3rd, Nickla, D.L., Ashby, R., Tkatchenko, A.V., Ostrin, L.A., Gawne,  
31 T.J., Pardue, M.T., Summers, J.A., Kee, C.S., Schroedl, F., Wahl, S., Jones, L., 2019. IMI -  
32 Report on Experimental Models of Emmetropization and Myopia. *Invest Ophthalmol Vis Sci*  
33 60, M31-M88.

34 Tummala, S.R., Neinstein, A., Fina, M.E., Dhingra, A., Vardi, N., 2014. Localization of  
35 Cacna1s to ON Bipolar Dendritic Tips Requires mGluR6-Related Cascade Elements. *Invest*  
36 *Ophthalmol Vis Sci* 55, 1483-1492.

37 Turkmen, S., Guo, G., Garshasbi, M., Hoffmann, K., Alshalah, A.J., Mischung, C., Kuss, A.,  
38 Humphrey, N., Mundlos, S., Robinson, P.N., 2009. CA8 mutations cause a novel syndrome  
39 characterized by ataxia and mild mental retardation with predisposition to quadrupedal gait.  
40 *PLoS Genet* 5, e1000487.

1 Umino, Y., Solessio, E., Barlow, R.B., 2008. Speed, spatial, and temporal tuning of rod and  
2 cone vision in mouse. *J. Neurosci.* 28, 189-198.

3 van Genderen, M.M., Bijveld, M.M., Claassen, Y.B., Florijn, R.J., Pearing, J.N., Meire,  
4 F.M., McCall, M.A., Riemsdag, F.C., Gregg, R.G., Bergen, A.A., Kamermans, M., 2009.  
5 Mutations in TRPM1 are a common cause of complete congenital stationary night blindness.  
6 *Am. J. Hum. Genet.* 85, 730-736.

7 van Mazijk, R., Haarman, A.E.G., Hoefsloot, L.H., Polling, J.R., van Tienhoven, M., Klaver,  
8 C.C.W., Verhoeven, V.J.M., Loudon, S.E., Thiadens, A., Kievit, A.J.A., 2022. Early onset X-  
9 linked female limited high myopia in three multigenerational families caused by novel  
10 mutations in the ARR3 gene. *Hum. Mutat.* 43, 380-388.

11 Van Schil, K., Karlstetter, M., Aslanidis, A., Dannhausen, K., Azam, M., Qamar, R., Leroy,  
12 B.P., Depasse, F., Langmann, T., De Baere, E., 2016. Autosomal recessive retinitis  
13 pigmentosa with homozygous rhodopsin mutation E150K and non-coding cis-regulatory  
14 variants in CRX-binding regions of SAMD7. *Sci Rep* 6, 21307.

15 Varin, J., 2020. Better understanding of the ON-bipolar cells signaling cascade and  
16 development of therapies for Congenital Stationary Night Blindness. PhD thesis.

17 Varin, J., Bouzidi, N., Dias, M.M.S., Pugliese, T., Michiels, C., Robert, C., Desrosiers, M.,  
18 Sahel, J.A., Audo, I., Dalkara, D., Zeitz, C., 2021a. Restoration of mGluR6 Localization  
19 Following AAV-Mediated Delivery in a Mouse Model of Congenital Stationary Night  
20 Blindness. *Invest Ophthalmol Vis Sci* 62, 24.

21 Varin, J., Bouzidi, N., Gauvin, G., Joffrois, T., Desrosiers, M., Robert, C., Miranda De Sousa  
22 Dias, M., Neullé, M., Michiels, C., Nassisi, M., Sahel, J.A., Picaud, S., Audo, I., Dalkara, D.,  
23 Zeitz, C., 2021b. Substantial restoration of night vision in adult mice with congenital  
24 stationary night blindness. *Molecular Therapy: Methods & Clinical Development*, in press.

25 Varin, J., Reynolds, M.M., Bouzidi, N., Tick, S., Wohlschlegel, J., Becquart, O., Michiels, C.,  
26 Dereure, O., Duvoisin, R.M., Morgans, C.W., Sahel, J.A., Samaran, Q., Guillot, B., Pulido,  
27 J.S., Audo, I., Zeitz, C., 2020. Identification and characterization of novel TRPM1  
28 autoantibodies from serum of patients with melanoma-associated retinopathy. *PLoS ONE* 15,  
29 e0231750.

30 Verhoeven, V.J., Hysi, P.G., Wojciechowski, R., Fan, Q., Guggenheim, J.A., Hohn, R.,  
31 MacGregor, S., Hewitt, A.W., Nag, A., Cheng, C.Y., Yonova-Doing, E., Zhou, X., Ikram,  
32 M.K., Buitendijk, G.H., McMahon, G., Kemp, J.P., Pourcain, B.S., Simpson, C.L., Makela,  
33 K.M., Lehtimäki, T., Kahonen, M., Paterson, A.D., Hosseini, S.M., Wong, H.S., Xu, L.,  
34 Jonas, J.B., Parssinen, O., Wedenoja, J., Yip, S.P., Ho, D.W., Pang, C.P., Chen, L.J., Burdon,  
35 K.P., Craig, J.E., Klein, B.E., Klein, R., Haller, T., Metspalu, A., Khor, C.C., Tai, E.S., Aung,  
36 T., Vithana, E., Tay, W.T., Barathi, V.A., Consortium for Refractive, E., Myopia, Chen, P.,  
37 Li, R., Liao, J., Zheng, Y., Ong, R.T., Doring, A., Diabetes, C., Complications  
38 Trial/Epidemiology of Diabetes, I., Complications Research, G., Evans, D.M., Timpson, N.J.,  
39 Verkerk, A.J., Meitinger, T., Raitakari, O., Hawthorne, F., Spector, T.D., Karssen, L.C.,  
40 Pirastu, M., Murgia, F., Ang, W., Wellcome Trust Case Control, C., Mishra, A., Montgomery,  
41 G.W., Pennell, C.E., Cumberland, P.M., Cotlarciuc, I., Mitchell, P., Wang, J.J., Schache, M.,  
42 Janmahasatian, S., Igo, R.P., Jr., Lass, J.H., Chew, E., Iyengar, S.K., Fuchs' Genetics Multi-  
43 Center Study, G., Gorgels, T.G., Rudan, I., Hayward, C., Wright, A.F., Polasek, O., Vataavuk,

1 Z., Wilson, J.F., Fleck, B., Zeller, T., Mirshahi, A., Muller, C., Uitterlinden, A.G.,  
2 Rivadeneira, F., Vingerling, J.R., Hofman, A., Oostra, B.A., Amin, N., Bergen, A.A., Teo,  
3 Y.Y., Rahi, J.S., Vitart, V., Williams, C., Baird, P.N., Wong, T.Y., Oexle, K., Pfeiffer, N.,  
4 Mackey, D.A., Young, T.L., van Duijn, C.M., Saw, S.M., Bailey-Wilson, J.E., Stambolian,  
5 D., Klaver, C.C., Hammond, C.J., 2013. Genome-wide meta-analyses of multiancestry  
6 cohorts identify multiple new susceptibility loci for refractive error and myopia. *Nat. Genet.*  
7 45, 314-318.

8 Veth, K.N., Willer, J.R., Collery, R.F., Gray, M.P., Willer, G.B., Wagner, D.S., Mullins,  
9 M.C., Udvadia, A.J., Smith, R.S., John, S.W., Gregg, R.G., Link, B.A., 2011. Mutations in  
10 zebrafish *lrp2* result in adult-onset ocular pathogenesis that models myopia and other risk  
11 factors for glaucoma. *PLoS Genet* 7, e1001310.

12 Vitale, S., Sperduto, R.D., Ferris, F.L., 3rd, 2009. Increased prevalence of myopia in the  
13 United States between 1971-1972 and 1999-2004. *Arch. Ophthalmol.* 127, 1632-1639.

14 Vocale, L.G., Crewther, S., Riddell, N., Hall, N.E., Murphy, M., Crewther, D., 2021. RNA-  
15 seq and GSEA identifies suppression of ligand-gated chloride efflux channels as the major  
16 gene pathway contributing to form deprivation myopia. *Sci Rep* 11, 5280.

17 Wakeham, C.M., Ren, G., Morgans, C.W., 2020. Expression and distribution of trophoblast  
18 glycoprotein in the mouse retina. *J. Comp. Neurol.* 528, 1660-1671.

19 Wakeham, C.M., Wilmarth, P.A., Cunliffe, J.M., Klimek, J.E., Ren, G., David, L.L.,  
20 Morgans, C.W., 2019. Identification of PKC $\alpha$ -dependent phosphoproteins in mouse  
21 retina. *J Proteomics* 206, 103423.

22 Wallman, J., Winawer, J., 2004. Homeostasis of eye growth and the question of myopia.  
23 *Neuron* 43, 447-468.

24 Wang, W.Y., Chen, C., Chang, J., Chien, L., Shih, Y.F., Lin, L.L.K., Pang, C.P., Wang, I.J.,  
25 2021. Pharmacotherapeutic candidates for myopia: A review. *Biomed. Pharmacother.* 133,  
26 111092.

27 Weinstein, B., Grether, W.F., 1940. A comparison of visual acuity in the rhesus monkey and  
28 man. *J Comp Physiol* 30, 187-195.

29 Westall, C.A., Dhaliwal, H.S., Panton, C.M., Sigesmun, D., Levin, A.V., Nischal, K.K.,  
30 Heon, E., 2001. Values of electroretinogram responses according to axial length. *Doc.*  
31 *Ophthalmol.* 102, 115-130.

32 Whitman, M.C., Miyake, N., Nguyen, E.H., Bell, J.L., Matos Ruiz, P.M., Chan, W.M., Di  
33 Gioia, S.A., Mukherjee, N., Barry, B.J., Bosley, T.M., Khan, A.O., Engle, E.C., 2019.  
34 Decreased ACKR3 (CXCR7) function causes oculomotor synkinesis in mice and humans.  
35 *Hum. Mol. Genet.* 28, 3113-3125.

36 Winkelman, B.H.J., Howlett, M.H.C., Holzel, M.B., Joling, C., Fransen, K.H., Pangen, G.,  
37 Kamermans, S., Sakuta, H., Noda, M., Simonsz, H.J., McCall, M.A., De Zeeuw, C.I.,  
38 Kamermans, M., 2019. Nystagmus in patients with congenital stationary night blindness  
39 (CSNB) originates from synchronously firing retinal ganglion cells. *PLoS Biol.* 17, e3000174.

1 Wisard, J., Faulkner, A., Chrenek, M.A., Waxweiler, T., Waxweiler, W., Donmoyer, C., Liou,  
2 G.I., Craft, C.M., Schmid, G.F., Boatright, J.H., Pardue, M.T., Nickerson, J.M., 2011.  
3 Exaggerated eye growth in IRBP-deficient mice in early development. *Invest Ophthalmol Vis*  
4 *Sci* 52, 5804-5811.

5 Witzel, D.A., Smith, E.L., Wilson, R.D., Aguirre, G.D., 1978. Congenital stationary night  
6 blindness: an animal model. *Invest Ophthalmol Vis Sci* 17, 788-795.

7 Wojciechowski, R., 2011. Nature and nurture: the complex genetics of myopia and refractive  
8 error. *Clin. Genet.* 79, 301-320.

9 Woods, S.M., Mountjoy, E., Muir, D., Ross, S.E., Atan, D., 2018. A comparative analysis of  
10 rod bipolar cell transcriptomes identifies novel genes implicated in night vision. *Sci Rep* 8,  
11 5506.

12 Wu, H., Chen, W., Zhao, F., Zhou, Q., Reinach, P.S., Deng, L., Ma, L., Luo, S., Srinivasalu,  
13 N., Pan, M., Hu, Y., Pei, X., Sun, J., Ren, R., Xiong, Y., Zhou, Z., Zhang, S., Tian, G., Fang,  
14 J., Zhang, L., Lang, J., Wu, D., Zeng, C., Qu, J., Zhou, X., 2018. Scleral hypoxia is a target  
15 for myopia control. *Proc Natl Acad Sci U S A* 115, E7091-E7100.

16 Wu, P.C., Tsai, C.L., Gordon, G.M., Jeong, S., Itakura, T., Patel, N., Shi, S., Fini, M.E.,  
17 2015a. Chondrogenesis in scleral stem/progenitor cells and its association with form-deprived  
18 myopia in mice. *Mol Vis* 21, 138-147.

19 Wu, P.C., Tsai, C.L., Wu, H.L., Yang, Y.H., Kuo, H.K., 2013. Outdoor activity during class  
20 recess reduces myopia onset and progression in school children. *Ophthalmology* 120, 1080-  
21 1085.

22 Wu, X.H., Li, Y.Y., Zhang, P.P., Qian, K.W., Ding, J.H., Hu, G., Weng, S.J., Yang, X.L.,  
23 Zhong, Y.M., 2015b. Unaltered retinal dopamine levels in a C57BL/6 mouse model of form-  
24 deprivation myopia. *Invest Ophthalmol Vis Sci* 56, 967-977.

25 Xiao, X., Li, S., Jia, X., Guo, X., Zhang, Q., 2016. X-linked heterozygous mutations in *ARR3*  
26 cause female-limited early onset high myopia. *Mol. Vis.* 22, 1257-1266.

27 Xiong, S., Sankaridurg, P., Naduvilath, T., Zang, J., Zou, H., Zhu, J., Lv, M., He, X., Xu, X.,  
28 2017. Time spent in outdoor activities in relation to myopia prevention and control: a meta-  
29 analysis and systematic review. *Acta Ophthalmol* 95, 551-566.

30 Xiong, W.H., Duvoisin, R.M., Adamus, G., Jeffrey, B.G., Gellman, C., Morgans, C.W., 2013.  
31 Serum TRPM1 autoantibodies from melanoma associated retinopathy patients enter retinal  
32 on-bipolar cells and attenuate the electroretinogram in mice. *PLoS ONE* 8, e69506.

33 Xu, X., Li, S., Xiao, X., Wang, P., Guo, X., Zhang, Q., 2009. Sequence variations of *GRM6*  
34 in patients with high myopia. *Mol. Vis.* 15, 2094-2100.

35 Xue, C., Wang, H.H., Zhu, J., Zhou, J., 2018. The expression patterns of vestigial like family  
36 member 4 genes in zebrafish embryogenesis. *Gene Expr. Patterns* 28, 34-41.

37 Yang, H.S., Vitaterna, M.H., Laposky, A.D., Shimomura, K., Turek, F.W., 2009. Genetic  
38 analysis of daily physical activity using a mouse chromosome substitution strain. *Physiol*  
39 *Genomics* 39, 47-55.



1 Ye, J., Shen, M., Huang, S., Fan, Y., Yao, A., Pan, C., Shi, X., Lu, F., Shao, Y., 2019. Visual  
2 Acuity in Pathological Myopia Is Correlated With the Photoreceptor Myoid and Ellipsoid  
3 Zone Thickness and Affected by Choroid Thickness. *Invest Ophthalmol Vis Sci* 60, 1714-  
4 1723.

5 Yip, S.P., Li, C.C., Yiu, W.C., Hung, W.H., Lam, W.W., Lai, M.C., Ng, P.W., Fung, W.Y.,  
6 Chu, P.H., Jiang, B., Chan, H.H., Yap, M.K., 2013. A novel missense mutation in the NYX  
7 gene associated with high myopia. *Ophthalmic Physiol. Opt.* 33, 346-353.

8 Yonehara, K., Fiscella, M., Drinnenberg, A., Esposti, F., Trenholm, S., Krol, J., Franke, F.,  
9 Scherf, B.G., Kusnyerik, A., Muller, J., Szabo, A., Juttner, J., Cordoba, F., Reddy, A.P.,  
10 Nemeth, J., Nagy, Z.Z., Munier, F., Hierlemann, A., Roska, B., 2016. Congenital Nystagmus  
11 Gene FRMD7 Is Necessary for Establishing a Neuronal Circuit Asymmetry for Direction  
12 Selectivity. *Neuron* 89, 177-193.

13 Young, T.L., 2009. Molecular genetics of human myopia: an update. *Optom. Vis. Sci.* 86, E8-  
14 E22.

15 Zacks, D.N., Han, Y., Zeng, Y., Swaroop, A., 2006. Activation of signaling pathways and  
16 stress-response genes in an experimental model of retinal detachment. *Invest Ophthalmol Vis*  
17 *Sci* 47, 1691-1695.

18 Zeitz, C., Jacobson, S.G., Hamel, C.P., Bujakowska, K., Neuille, M., Orhan, E., Zanolghi,  
19 X., Lancelot, M.E., Michiels, C., Schwartz, S.B., Bocquet, B., Congenital Stationary Night  
20 Blindness, C., Antonio, A., Audier, C., Letexier, M., Saraiva, J.P., Luu, T.D., Sennlaub, F.,  
21 Nguyen, H., Poch, O., Dollfus, H., Lecompte, O., Kohl, S., Sahel, J.A., Bhattacharya, S.S.,  
22 Audo, I., 2013. Whole-exome sequencing identifies LRIT3 mutations as a cause of  
23 autosomal-recessive complete congenital stationary night blindness. *Am. J. Hum. Genet.* 92,  
24 67-75.

25 Zeitz, C., Robson, A.G., Audo, I., 2015. Congenital stationary night blindness: an analysis  
26 and update of genotype-phenotype correlations and pathogenic mechanisms. *Prog. Retin. Eye*  
27 *Res.* 45, 58-110.

28 Zeitz, C., van Genderen, M., Neidhardt, J., Luhmann, U.F., Hoeben, F., Forster, U., Wycisk,  
29 K., Matyas, G., Hoyng, C.B., Riemsdag, F., Meire, F., Cremers, F.P., Berger, W., 2005.  
30 Mutations in GRM6 cause autosomal recessive congenital stationary night blindness with a  
31 distinctive scotopic 15-Hz flicker electroretinogram. *Invest Ophthalmol Vis Sci* 46, 4328-  
32 4335.

33 Zhang, Q., Xiao, X., Li, S., Jia, X., Yang, Z., Huang, S., Caruso, R.C., Guan, T., Sergeev, Y.,  
34 Guo, X., Hejtmancik, J.F., 2007. Mutations in NYX of individuals with high myopia, but  
35 without night blindness. *Mol. Vis.* 13, 330-336.

36 Zhou, G., Strom, R.C., Giguere, V., Williams, R.W., 2001. Modulation of retinal cell  
37 populations and eye size in retinoic acid receptor knockout mice. *Mol Vis* 7, 253-260.

38 Zhou, L., Li, T., Song, X., Li, Y., Li, H., Dan, H., 2015. NYX mutations in four families with  
39 high myopia with or without CSNB1. *Mol. Vis.* 21, 213-223.

Zhou, L., Li, T., Xing, Y.Q., Li, Y., Wu, Q.S., Zhang, M.J., 2016. Novel TRPM1 mutations in two Chinese families with early-onset high myopia, with or without complete congenital stationary night blindness. *Int J Ophthalmol* 9, 1396-1402.

Zhou, X., Huang, Q., An, J., Lu, R., Qin, X., Jiang, L., Li, Y., Wang, J., Chen, J., Qu, J., 2010. Genetic deletion of the adenosine A2A receptor confers postnatal development of relative myopia in mice. *Invest Ophthalmol Vis Sci* 51, 4362-4370.

Zhou, X., Pardue, M.T., Iuvone, P.M., Qu, J., 2017. Dopamine signaling and myopia development: What are the key challenges. *Prog. Retin. Eye Res.* 61, 60-71.

Zhu, J.Y., Lin, S., Ye, J., 2018. YAP and TAZ, the conductors that orchestrate eye development, homeostasis, and disease. *J. Cell. Physiol.* 234, 246-258.

## Figures legends:

**Figure 1:** Schematic representation of ERG recordings of five different species known to display a cCSNB phenotype. This figure was taken from the PhD thesis of Juliette Varin (Varin, 2020), which in turn was adapted from Audo *et al.*, 2009 (for human CSNB, subject with mutations in *TRPM1*) from Sandmeyer *et al.*, 2007 (for the *TRPM1*<sup>-/-</sup> Appaloosa horse ERG), from Kondo *et al.*, 2015 (for the *LRIT3*<sup>-/-</sup> Beagle dog ERG), from Pardue *et al.*, 1998 (for the *Nyx*<sup>-/-</sup> mouse ERG) and from Peachey *et al.*, 2012 (for the MO-gpr179 zebrafish ERG).

**Figure 2:** Example of scotopic electroretinograms in mice lacking *Aplp2*, a gene associated with myopia in humans. Lack of *Aplp2* causes a dose-dependent decrease in the b-wave amplitude (A). The b-wave implicit time was increased in mice lacking *Aplp2*. Lack of *Aplp2* did not have a significant impact on either a-wave amplitude or a-wave implicit time. Lack of *Aplp2* caused a decrease in amplitude and an increase of the implicit time of the oscillatory potentials (B). Figure was taken from Tkatchenko *et al.*, 2015 (Tkatchenko *et al.*, 2015) with permission.

1

2 **Figure 3:** Lens-induced myopia in wild-type mice measured after three weeks of goggling.  
3 Myopia can be induced in mice using in-house-made goggles with negative spectacle lenses  
4 and induced refractive error can be measured using an automated photorefractor (Schaeffel et  
5 al., 2004). Wild-type mice (n=12) were goggled at P21 for three weeks. The goggles were  
6 fitted with -25.00 D lenses for the right eyes (RE) and no lens for the left eyes (LE), which  
7 were used as controls. The interocular differences between treated and control eyes was  
8 measured at P21 before goggle application and after goggle application at P42. Statistical  
9 significance was obtained with p-values, where  $p \leq 0.05 = *$ ,  $p \leq 0.01 = **$  and  $p \leq 0.001 = ***$ .

10

11 **Figure 4:** Reduced retinal DOPAC and DA in light adapted cCSNB mouse models lacking  
12 *Gpr179*, *Lrit3* and *Grm6* statistically analyzed using the Mann-Whitney test. Values are  
13 reported as standard deviations. Statistical significance was obtained with p-values, where  $p \leq$   
14  $0.05 = *$ ,  $p \leq 0.01 = **$  and  $p \leq 0.001 = ***$ .

15

16 **Figure 5:** A, Venn diagram of differentially expressed genes (DEGs) in the retina of three  
17 cCSNB mouse lines identified by RNA-Seq analysis. This revealed 155 (green), 133 (red),  
18 and 222 (blue) DEGs for *Gpr179*, *Lrit3* and *Grm6* mice, respectively. Of those, 7 DEGs were  
19 common to all three cCSNB mice, and 38 DEGs were shared by the *Gpr179* and *Lrit3* mice.  
20 B, Hierarchical clustering analysis of the 52 DEGs present in at least two mouse lines  
21 identified 10 clusters (different colors left column). The *z-score* was derived from the average  
22 of the replicates for each experimental group. Blue: low expression; orange: high expression.  
23 The largest cluster consists of genes less expressed in the cCSNB models (cluster 1).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24

**Figure 6:** Examples of genes found to be differentially expressed in three (red) and two (green) cCSNB mouse lines by RNA-Seq studies and validated by RT-qPCR experiments. Green boxes indicate the genes differentially expressed in two cCSNB mouse lines. Some genes appeared to be significantly differentially expressed only in two cCSNB mouse lines by RNA-Seq investigations, but were significantly differentially expressed in all three mouse lines by RT-qPCR studies (e.g. *Prkca* and *Tpbp*). Other genes appeared to be significantly differentially expressed in three cCSNB mouse lines by RNA-Seq investigations, but were statistically significantly differentially expressed only in two mouse lines by RT-qPCR studies (e.g. *Frem3* and *Ptprr*). Data were tested for normality and analyzed using the nonparametric Mann-Whitney test to compare expression. Values are reported as standard deviations. Statistical significance was obtained with p-values, where  $p \leq 0.05$ =\* and  $p \leq 0.01$  = \*\*. NRQ = Normalized relative quantity.

**Figure 7:** Interdependence of expression between genes implicated in cCSNB at the transcriptional level. There was a trend that *Trpm1* expression is dependent on the expression of *Gpr179*, *Lrit3* and *Grm6*, and that *Grm6* expression is dependent on the expression of *Lrit3*.

**Figure 8:** Schematic drawing (created with BioRender.com) of differentially expressed genes (DEGs), localization of their expression in the retina and their association with myopia. Genes in the white box, also appeared in myopia databases and were found to be differentially expressed in at least one cCSNB mouse line. They show expression in the retina although in which cell type remains uncharacterized.

1

2 **Figure 9:** Schematic representation of the DEG expression in the different types of BCs.  
3 BC1-4 = OFF-BCs, BC5-BC7 = ON-BCs (generated using the data from Shekhar et al., 2016  
4 (Shekhar et al., 2016) .

5

6 **Figure 10:** A, DEGs were enriched in different pathways, including the MAPK signaling  
7 pathway, synapse, GPCR ligand binding, eye development, endoderm and connective tissue  
8 pathways. B, Circle presentation showed that most of the DEGs appeared in multiple  
9 pathways.

10

11 **Figure 11:** Schematic drawing of DEGs (shown in brown) enriched in the MAPK signaling  
12 pathway (created with BioRender.com).

13

14 **Figure 12:** Quantification of western blot analyses for proteins for which RNA-Seq studies  
15 showed differential expression by RNA-Seq and RT-qPCR studies in *Gpr179*<sup>-/-</sup>, *Lrit3*<sup>-/-</sup> and  
16 *Grm6*<sup>-/-</sup> cCSNB mouse models (n ≥ 4). The protein amounts were normalized against  
17 GAPDH, visualized with Image J and statistically analyzed using the Mann-Whitney test.  
18 Values are reported as standard deviations. Statistical significance was obtained with p-  
19 values, where  $p \leq 0.05 = *$  and  $p \leq 0.01 = **$ .

20

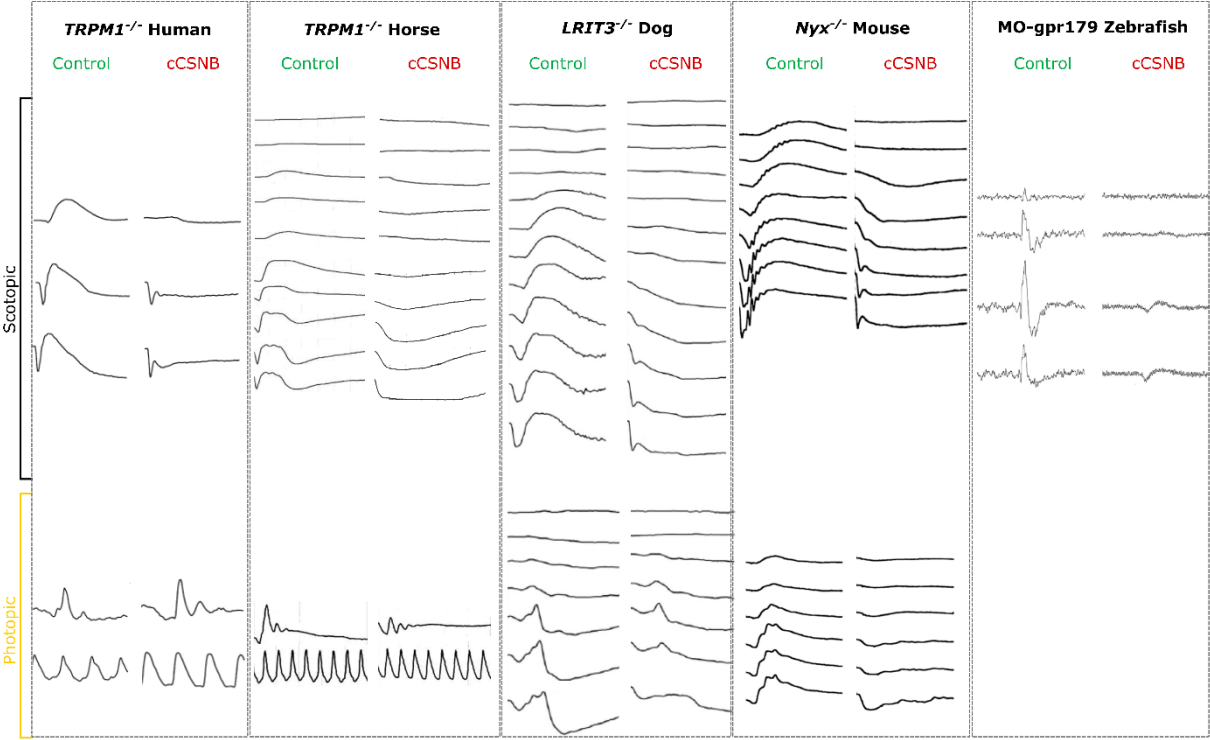
21 **Figure 13:** Immunostaining in *Gpr179*<sup>-/-</sup>, *Lrit3*<sup>-/-</sup> and *Grm6*<sup>-/-</sup> cCSNB mouse models showed a  
22 reduction of TPBG and PRKCA immunofluorescence in mice lacking *Gpr179* and *Lrit3* but

not in mice lacking *Grm6*. This was most obvious in the OPL and IPL (bar = 20  $\mu$ m). Phr = photoreceptor layer; ONL = outer nuclear layer; OPL = outer plexiform layer; inner nuclear layer; IPL = inner plexiform layer; GCL = ganglion cell layer.

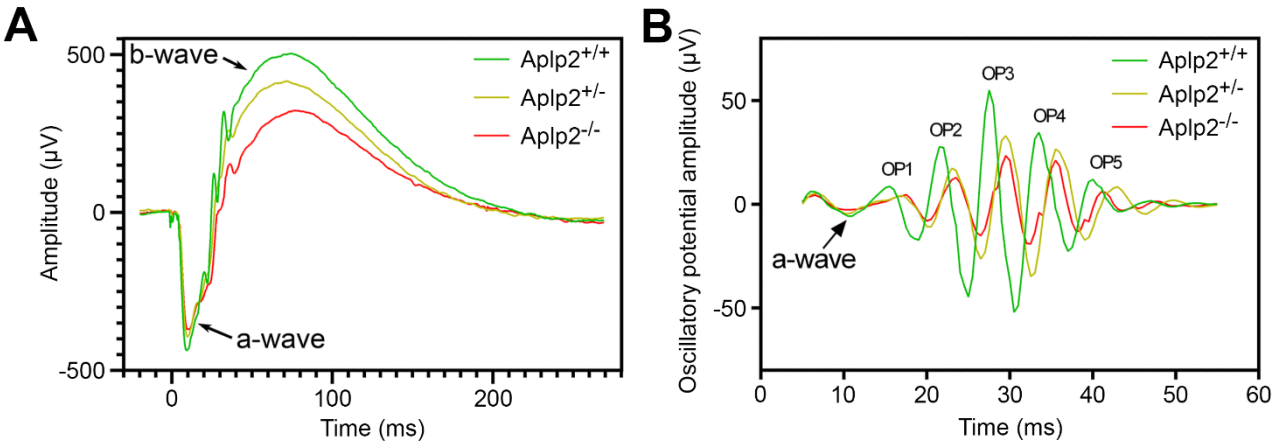
**Figure 14:** Quantification of all cell nuclei stained with DAPI revealed an equal number of cell nuclei in the inner nuclear layer (INL) in the mutant versus wild-type cCSNB mouse models (n = 3-8).

**Figure 15:** Quantification of all TH-positive cells revealed no significant differences between *Gpr179*<sup>+/+</sup> and *Gpr179*<sup>-/-</sup> (n=4 mice).

**Figure 1**

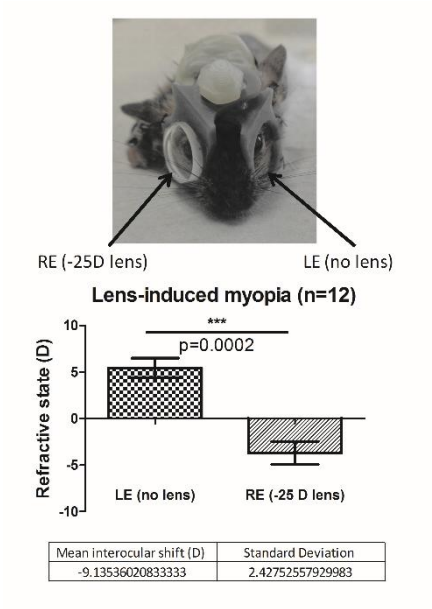


**Figure 2**



1

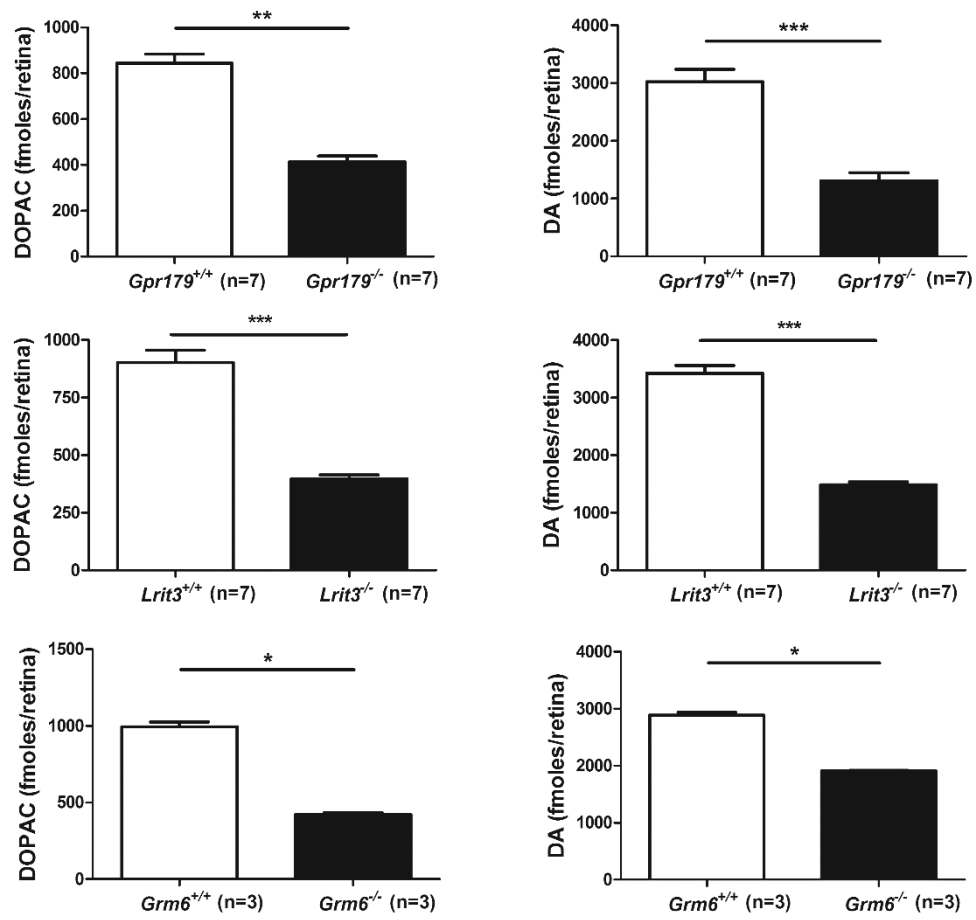
2 **Figure 3**



3

4 **Figure 4**

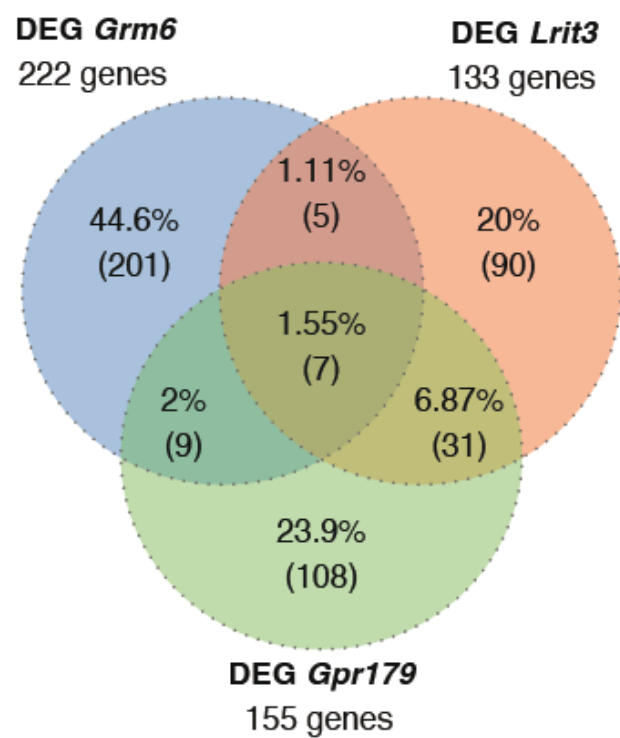




1

2 **Figure 5**

5A



5B

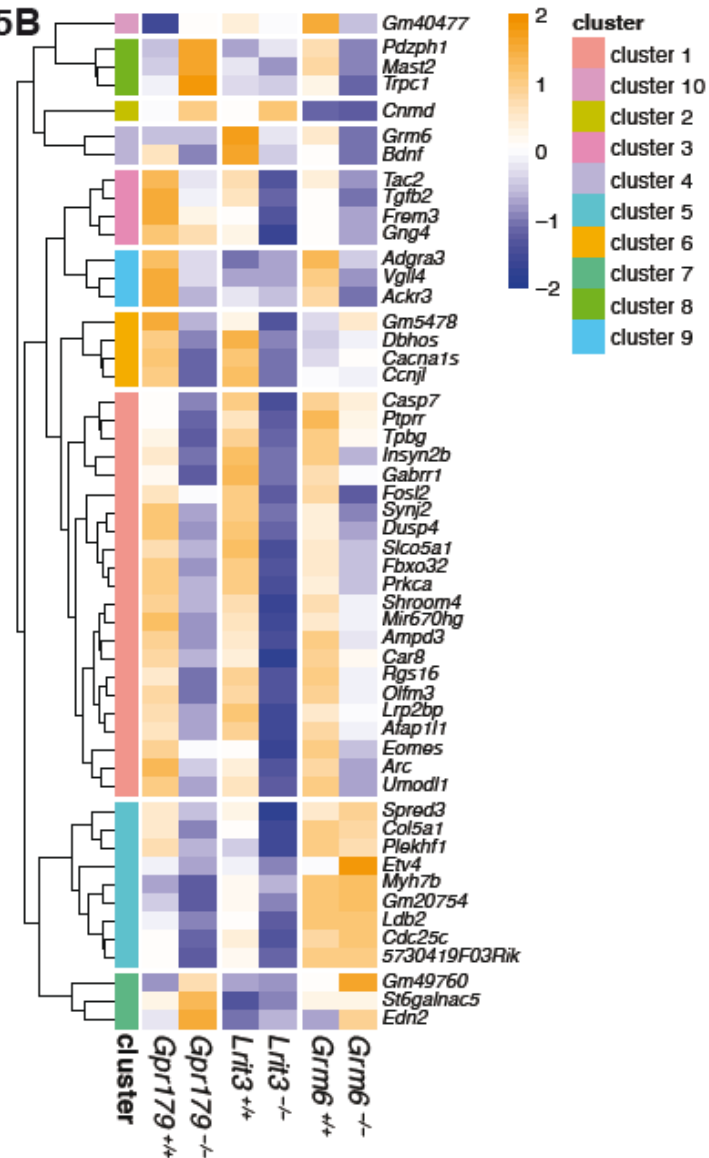
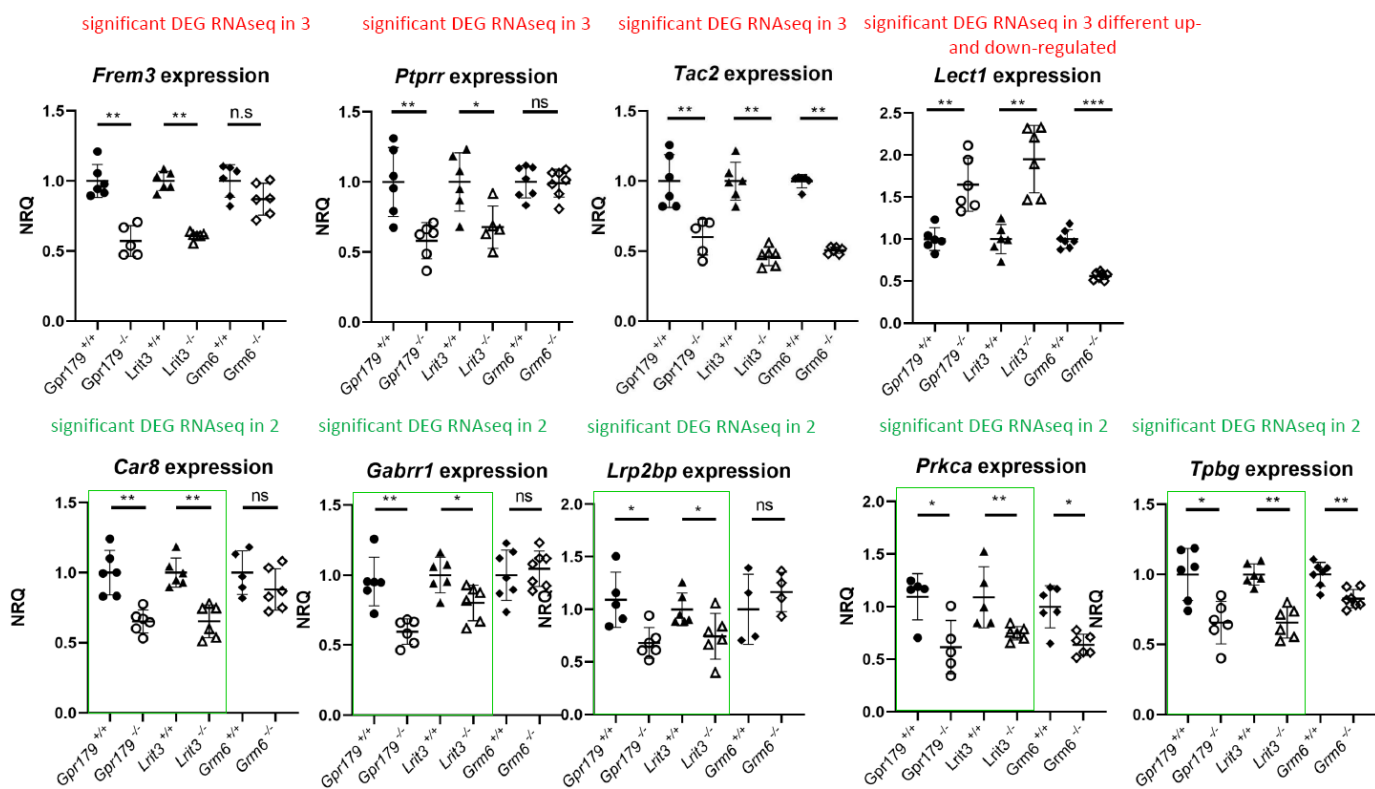


Figure 6

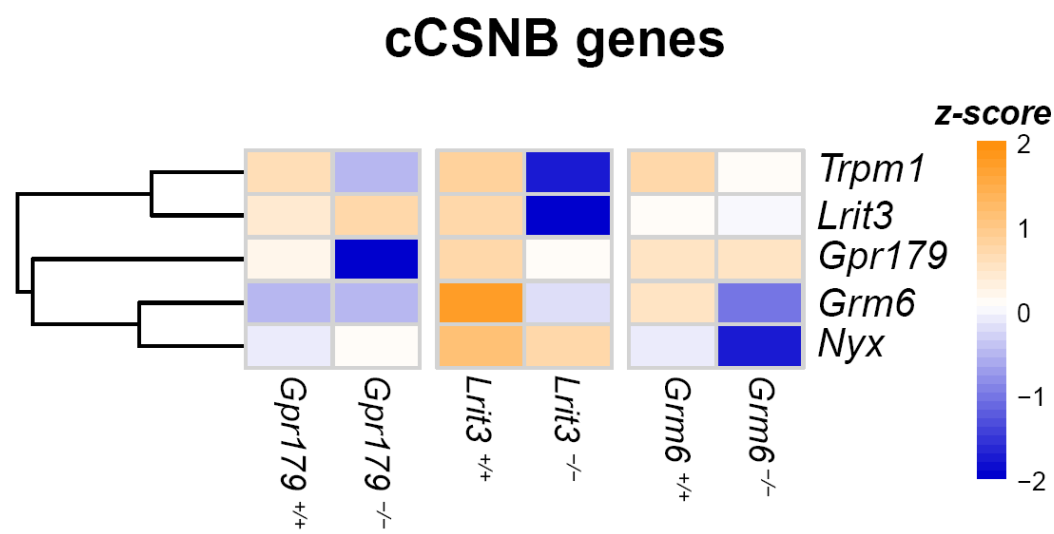
1



2

3

4 **Figure 7**



5

6 **Figure 8**

The eye with focus on the retina

Different retina cell types

DEGs in cCSNB

DEGs in cCSNB and associated with myopia

DEGs in cCSNB, associated with myopia and expressed in the retina

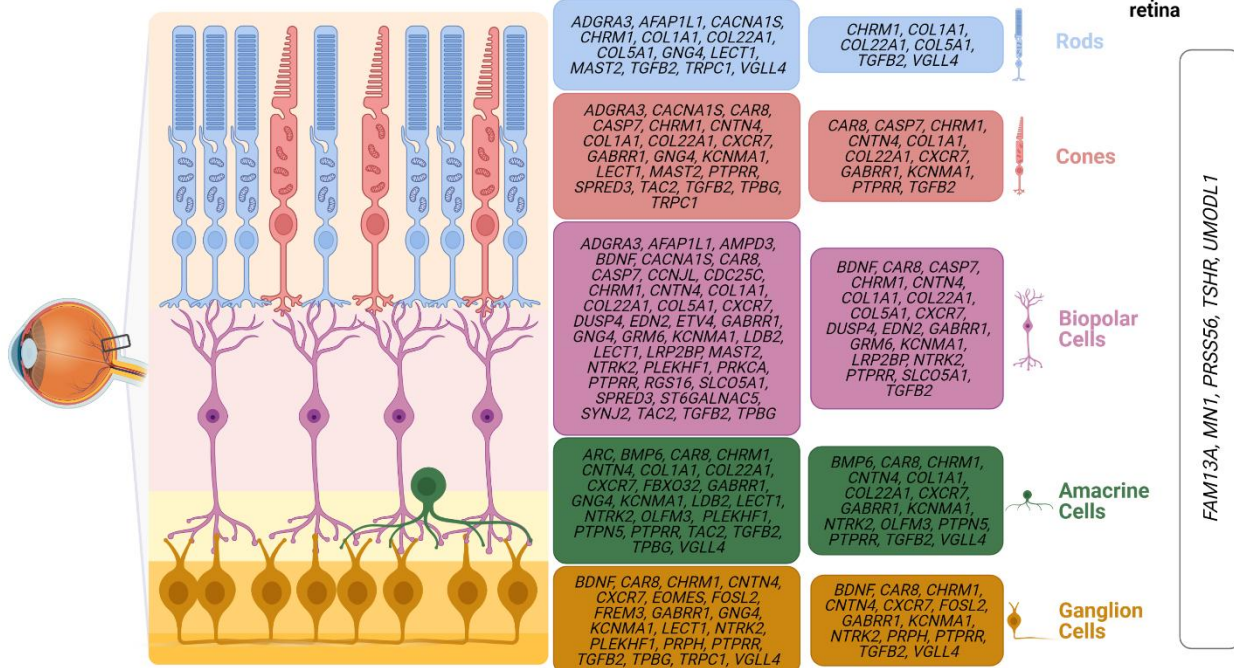
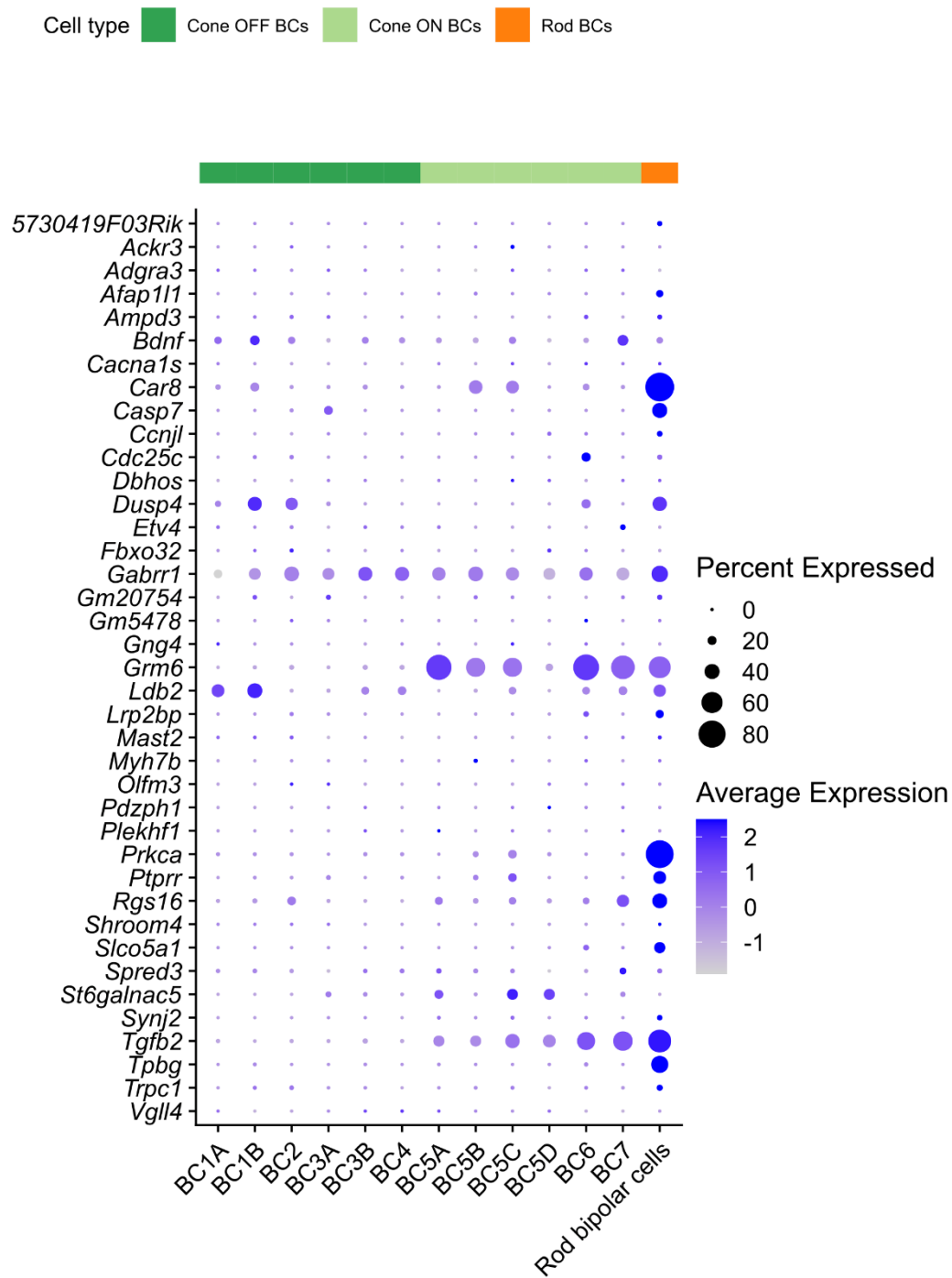


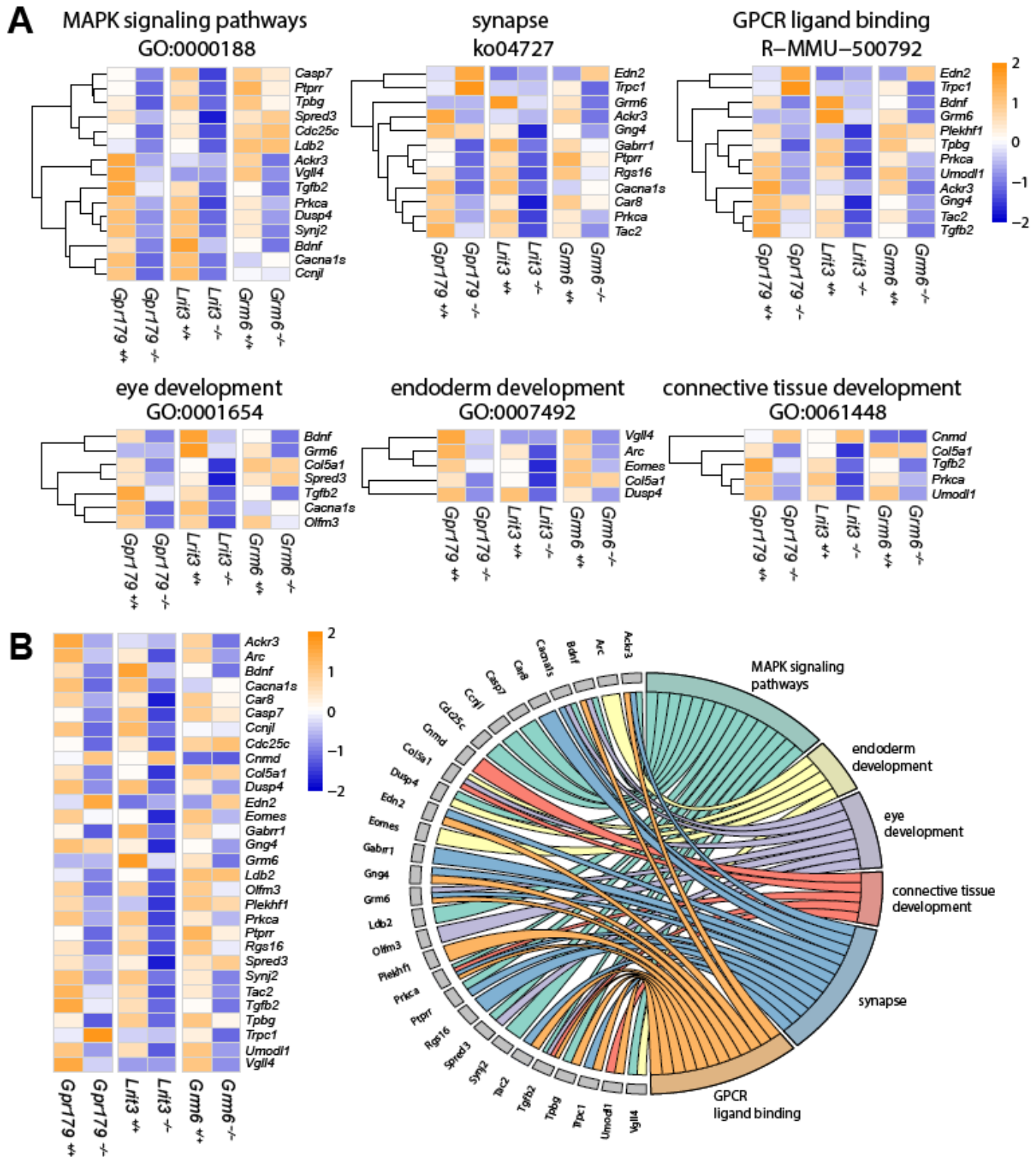
Figure 9



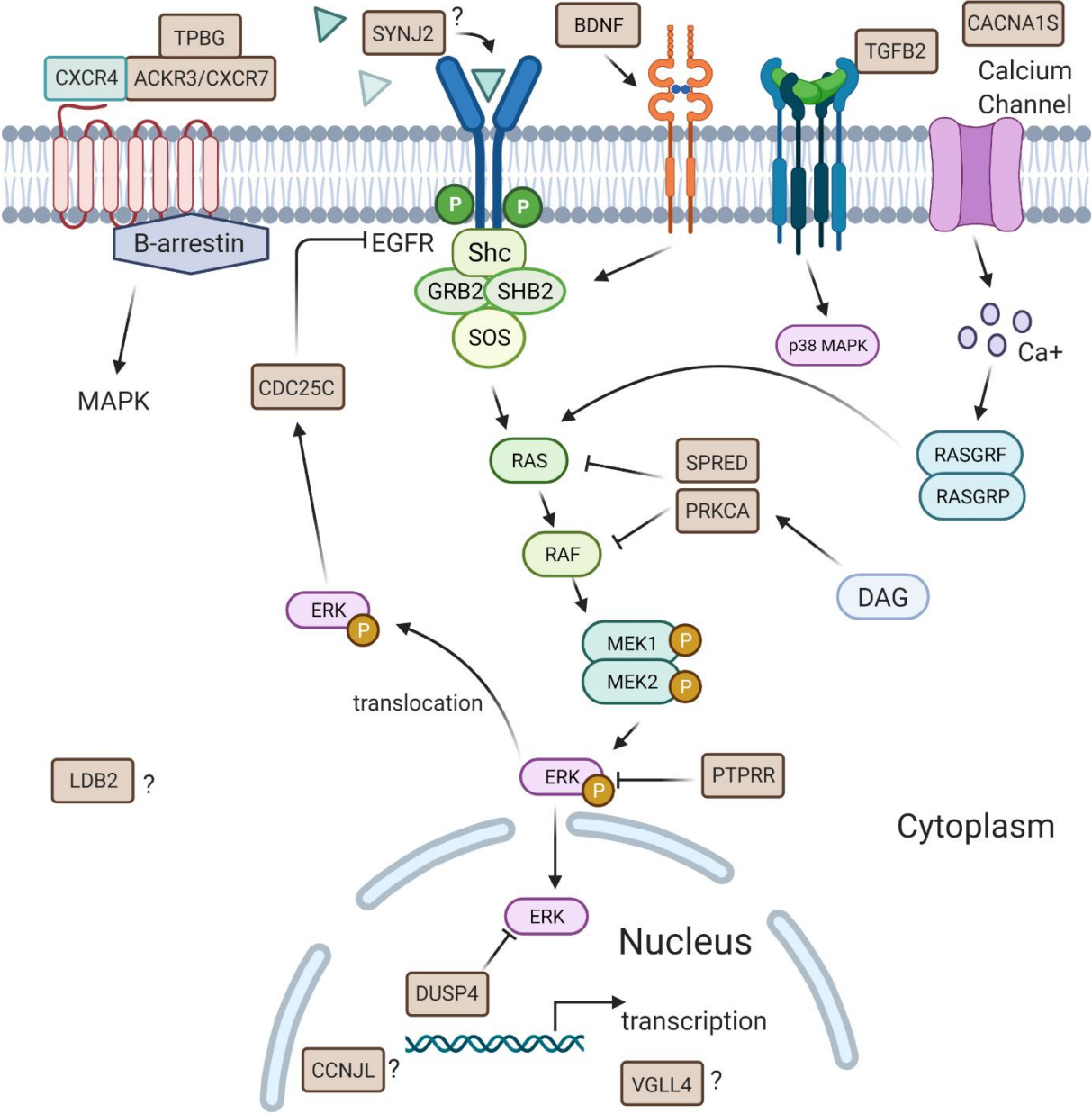
1

2

3 **Figure 10**



1    Figure 11



2

3

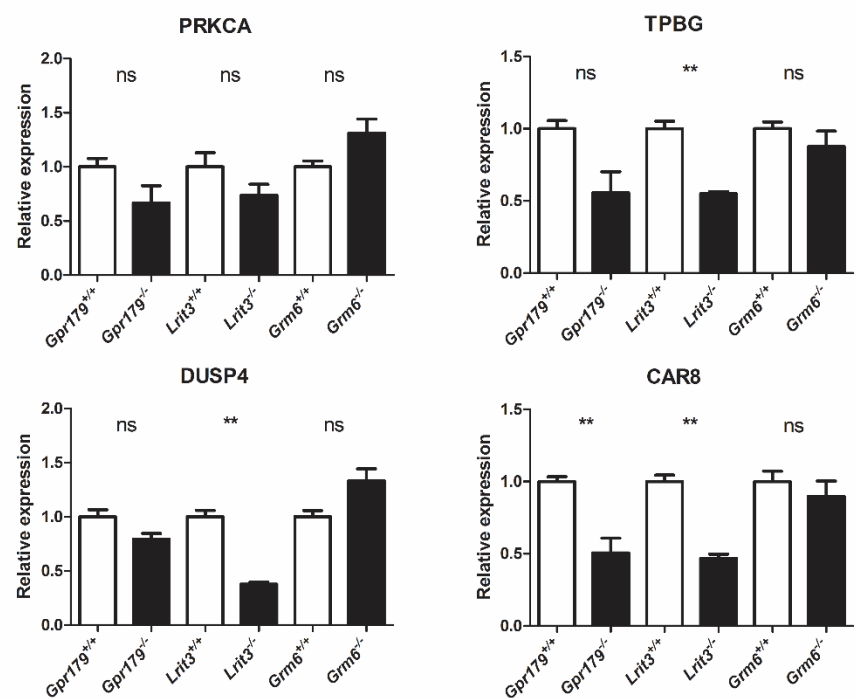
4

5

6

7

1 **Figure 12**



2

3

4

5

6

7

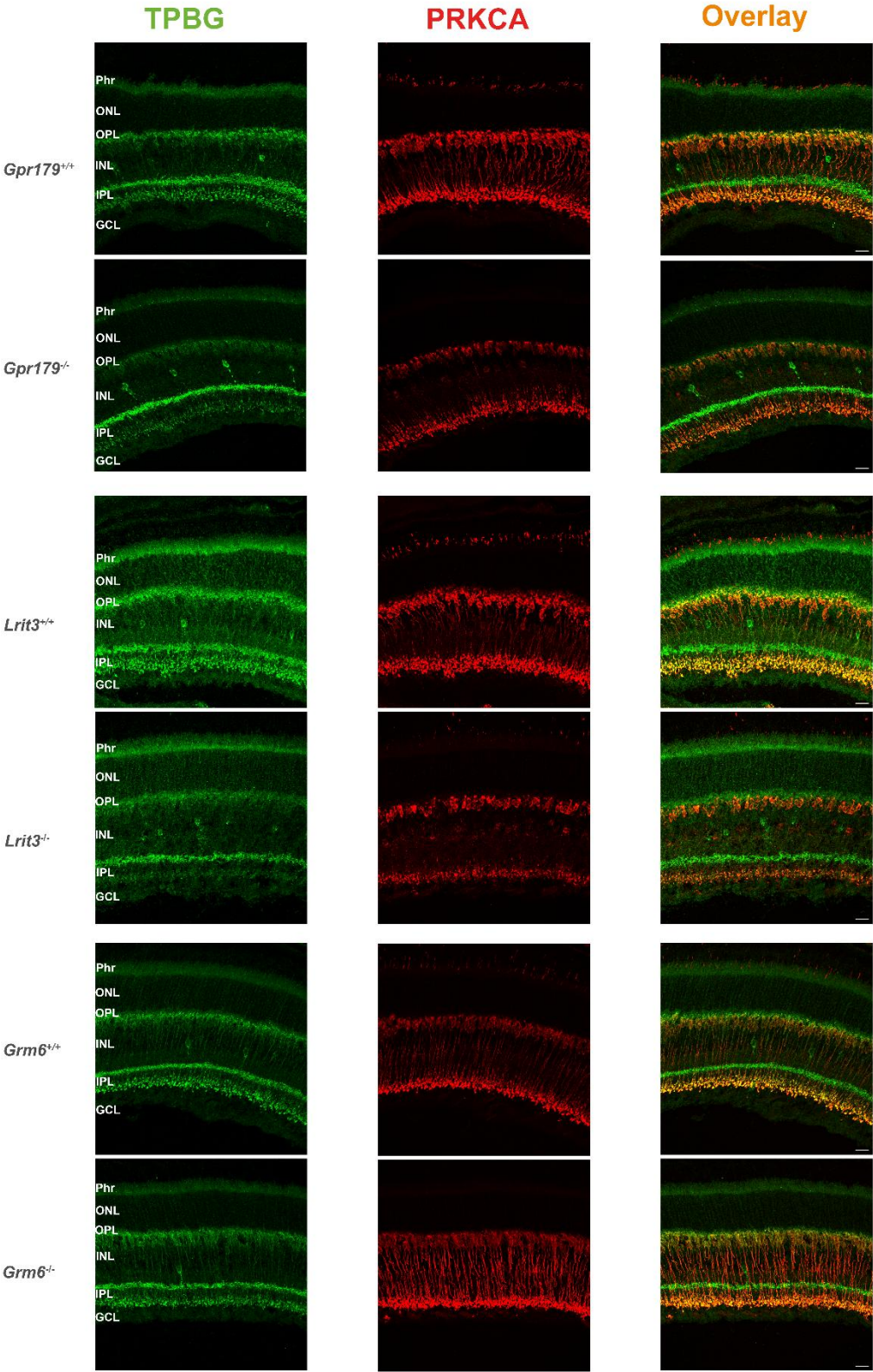
8

9

10



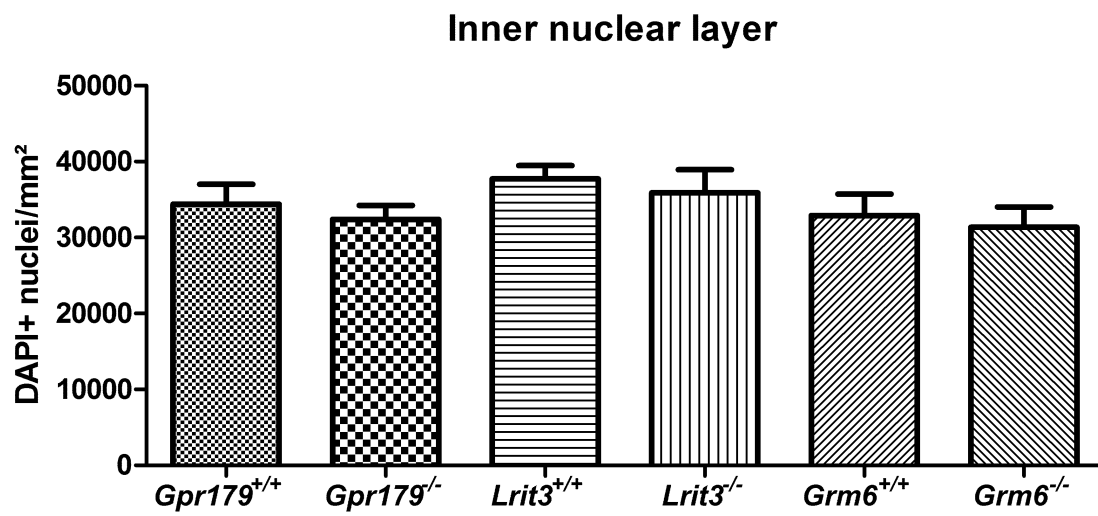
1    **Figure 13**



2

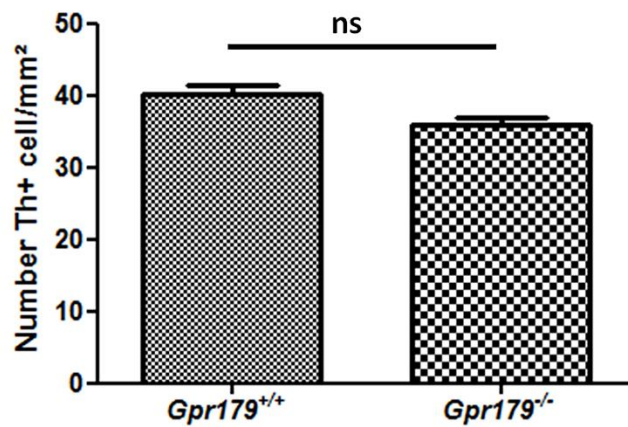
3

1 Figure 14



2

3 Figure 15



4