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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.

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1 **TITLE**

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

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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*^{-/-}, *Lrit3*^{-/-} and *Grm6*^{-/-}), 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	Keywords: congenital stationary night blindness, myopia, retina, transcriptome sequencing,
77	meta-analysis
78	
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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).

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

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

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

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

232

233 Studies in chicken and mice showed that light dependent ON-bipolar cell (BC) dopamine
234 signaling is a major player in the development and protection of myopia (Boatright et al.,
235 1994; Boelen et al., 1998; Dumitrescu et al., 2009; Iuvone et al., 1978; Schaeffel and
236 Feldkaemper, 2015; Stone et al., 2011). Retinal dopamine content is decreased in the absence
237 of light and during myopia development (Schaeffel and Feldkaemper, 2015). It was shown,
238 that intravitreal or topical application of levodopa, which is widely used in the treatment of
239 neurological disorders involving dysregulation of the dopaminergic system, inhibits the

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

245 Patients with **complete congenital stationary night blindness (cCSNB)**, which represents a
246 complete ON-BC dysfunction, with unaltered OFF-BC function present as well with high
247 myopia (median error of -7.4 D) (Bijveld et al., 2013; Zeitz et al., 2015). Multiple mutations
248 in cCSNB-associated genes such as *NYX*, *GRM6*, *GPR179*, *TRPM1* and *LRIT3* lead to this
249 condition in patients and mouse models (Audo et al., 2012; Bech-Hansen et al., 2000; Dryja et
250 al., 2005; Gregg et al., 2003; Koike et al., 2010; Li et al., 2009; Maddox et al., 2008; Masu et
251 al., 1995; Morgans et al., 2009; Neuille et al., 2014; Orhan et al., 2021; Orlandi et al., 2012;
252 Pardue and Peachey, 2014; Peachey et al., 2012; Pusch et al., 2000; Qian et al., 2015; van
253 Genderen et al., 2009; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2015; Zeitz et al., 2005).
254 cCSNB mouse models lacking *Nyx* (*nob*) and *Grm6* with ON-BC dysfunction, showed
255 **increased susceptibility to myopia and decreased dopamine content** (Chakraborty et al.,
256 2015; Pardue et al., 2008). While human subjects with cCSNB and high myopia have no **ON-**
257 **BC transmission**, their OFF-BC transmission is largely intact (Miyake et al., 1986; Zeitz et
258 al., 2015). By contrast, subjects with incomplete CSNB (iCSNB) show variable degrees of
259 myopia (median refractive error of -4.8 D), associated with both reduced ON-and OFF-
260 pathway dysfunction (Bijveld et al., 2013; Miyake et al., 1986; Zeitz et al., 2015). We are not
261 aware that high myopia has been reported with other forms of CSNB, leading to a rod
262 dysfunction and a Riggs-ERG (Zeitz et al., 2015). Aleman et al showed that stimulation of the
263 ON-pathway may thicken the choroid and thus perhaps inhibit myopia in humans (Aleman et

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

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

279

280 **2. Phenotype in human cases and animal models with complete congenital** 281 **stationary night blindness (cCSNB) and associated myopia**

282 **2.1. Signal transmission from photoreceptors to ON-bipolar cells**

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

287 the absence of the b-wave in dark adapted conditions (DA 0.01) (Figure 1). In light-adapted
288 conditions (LA 3.0 30 Hz and LA 3.0), ERGs are altered differently (see for details (Zeitz et
289 al., 2015)) (Figure 1). ERG findings under scotopic conditions highlight similarities between
290 cCSNB animal models and the human phenotype. In contrast, under photopic conditions,
291 cCSNB animal models show more variability between species (Figure 1). The photopic ERG
292 phenotype of cCSNB mouse models is generally more severe, including the absence of the b-
293 wave, compared to that of human cases or larger animal models (Figure 1) (e.g. (Neuille et al.,
294 2014; Orhan et al., 2021)). In contrast, cone-driven responses are comparable between CSNB
295 dogs, horses and human cases, i.e. mildly reduced and delayed (reviewed in (Kondo et al.,
296 2015; Varin et al., 2021b; Witzel et al., 1978; Zeitz et al., 2015) (Figure 1). These differences
297 may be a result of species-specific physiological differences, but could also be due to the use
298 of different ERG protocols (Varin et al., 2021b).

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

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

318

319

320 **2.2. Visual acuity in cCSNB and myopia**

321 Subjects with cCSNB have decreased visual acuity with a median of 0.30 log MAR
322 (Minimum Angle of Resolution; about 20/40) (Zeitz et al., 2015). Relatively preserved mean
323 best corrected visual acuity of 0.02 log MAR (about 20/20; (Ye et al., 2019)) and 0.88
324 decimals (better than 20/25; (Liu et al., 2010)) is observed in myopic (including high myopic)
325 subjects without underlying retinal changes. Pathologic myopia, however, is associated with a
326 reduced mean best corrected visual acuity of 0.56 ± 0.35 decimals (about 20/35; (Liu et al.,
327 2010)) and 0.19 ± 0.20 log MAR (about 20/30; (Ye et al., 2019)). About 30% of cases with
328 myopic retinal changes have visual acuity worse than 20/60. Hence, although cCSNB subjects
329 demonstrate high axial myopia (Al-Hujaili et al., 2019) their visual acuity loss is generally
330 more severe, due to cone ON-bipolar cell dysfunction, than in subjects with isolated myopia.

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

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

340 **2.3. Retinal structure in cCSNB and myopia**

341 In contrast to progressive rod-cone dystrophy, the retinal structure is quite well preserved in
342 human subjects with cCSNB. This is due to the stationary, functional, but not degenerative
343 nature of disease of cCSNB. A few reports describe thinning of inner retinal layers (INLs) in
344 cases with cCSNB as measured by spectral domain Optical Coherence Tomography (SD-
345 OCT). However, this thinning is different from that observed in subjects with progressive rod-
346 cone dystrophy (Al Oreany et al., 2016; Godara et al., 2012; Ivanova et al., 2019). SD-OCT
347 measurements done in the *Lrit3* mouse model of cCSNB also revealed thinning of the INL
348 (Neuille et al., 2014). It is not clear if the INL thinning observed in human cCSNB subjects
349 and in a few mouse models is related to the development of high myopia or if it is only caused
350 by the mutated gene causing cCSNB. A systematic analysis of cCSNB cases compared to
351 myopia control cohorts is needed to determine the exact cause of this thinning (Zeitz et al.,
352 2015).

353 In subjects with myopia without outer retinal changes, regional changes in central retinal
354 thickness have been described by SD-OCT; these include thinning of the INL and outer nuclear
355 layer, and thickening of OPL and photoreceptor outer segments (Liu et al., 2015; Ye et al.,
356 2019). In subjects with pathologic myopia, additional changes described under the term of
357 myopic maculopathy are observed (Ohno-Matsui et al., 2016).

358

359 **3. Studying myopia in mouse models**

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

367 The mouse, has become a popular animal model for the myopia research (Barathi et al., 2014;
368 Barathi et al., 2013; Beleggia et al., 2015; Cases et al., 2015; Hudson et al., 2015; Ma et al.,
369 2014; Miyake et al., 2015; Pardue et al., 2008; Song et al., 2016; Storm et al., 2014; Tekin et
370 al., 2013; Tkatchenko et al., 2012; Tkatchenko et al., 2015; Tran-Viet et al., 2013; Wu et al.,
371 2015a; Wu et al., 2015b). The mouse offers a number of important advantages compared to
372 other species, including well-established techniques allowing the alteration of its genome.
373 Moreover, both genes and environment can be manipulated in the same mouse (Barathi et al.,
374 2008; Schaeffel et al., 2004; Tejedor and de la Villa, 2003a; Tkatchenko et al., 2010).
375 Behavioral studies suggest that vision is critical for accurate spatial navigation in mice (Buhot
376 et al., 2001; Cook et al., 2001; de la Cera et al., 2006; Faulstich et al., 2004). Although mice
377 are classified as nocturnal animals they are also active during the day and have diurnal retinal
378 features (Flores et al., 2007; Jacobs, 2013; Yang et al., 2009). Mice undergo emmetropization
379 driven by photopic visual stimulation similar to humans (Tkatchenko et al., 2013). Basic
380 spatial and temporal vision characteristics in mice are similar to those in humans (Histed et
381 al., 2012; Umino et al., 2008) but with lower visual function compared to humans (Prusky and
382 Douglas, 2004). Due to the above-mentioned differences, thresholds for rod-dominated

383 (scotopic) and cone-dominated (photopic) vision in mice, as well as the structure of the retinal
384 scotopic and photopic pathways, maybe different but still show high similarities to those in
385 humans (Leamey et al., 2008; Umino et al., 2008). Although mice lack the *fovea* found in
386 primates, the mouse retina has an area of increased density of photoreceptors and retinal
387 ganglion cells (RGC) just temporal to the optic disc, which represents an anatomical and
388 functional analog of the *area centralis* found in all non-primate mammals (Drager and Olsen,
389 1981; Jeon et al., 1998; Leamey et al., 2008). Induced changes in genetic background and
390 gene-targeted mutations affect refractive eye development and susceptibility to myopia in
391 mice (Schippert et al., 2007; Tkatchenko et al., 2015; Tkatchenko et al., 2019; Troilo et al.,
392 2019; Wisard et al., 2011; Zhou et al., 2001; Zhou et al., 2010). Experimental myopia can be
393 induced in mice using visual **form deprivation (form deprivation myopia, FDM)** or
394 **negative spectacle lenses (lens-induced myopia, LIM)**, similar to other animal models
395 (Chakraborty et al., 2014a; Pardue et al., 2008; Pardue et al., 2013; Park et al., 2013;
396 Schaeffel et al., 2004; Tejedor and de la Villa, 2003b; Tkatchenko et al., 2015) (Figure 3).

397 Susceptibility to FDM was increased in mouse models with a defect in the ON-pathway
398 (Chakraborty et al., 2015; Pardue et al., 2008), highlighting that ON-pathway disruption may
399 be an important element in refractive error development. More specifically, **cCSNB-**
400 **associated myopia** as shown by myopic shifts in eyes with FDM was observed in mice
401 lacking *Nyx* (nob) (Gregg et al., 2003) and *Grm6* (Masu et al., 1995) (Chakraborty et al.,
402 2015; Pardue et al., 2008). We hypothesize that the cCSNB models used in the present study
403 will similarly show a greater susceptibility to FDM- or LIM-induced myopia, although the
404 genetic background of the mice must be considered, as this can strongly influence both the
405 baseline and susceptibility to induced myopia. For example, wild-type mice in a “129
406 background” show high baseline myopia (~ -20D) compared to those in a C57BL/6J
407 background (Tkatchenko et al., 2019). Our cCSNB models lacking *Gpr179* and *Lrit3* are in a

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

414 All cCSNB mouse models share the same gene defects as human subjects with cCSNB (Audo
415 et al., 2012; Bech-Hansen et al., 2000; Dryja et al., 2005; Gregg et al., 2003; Pardue et al.,
416 1998; Peachey et al., 2012; Pusch et al., 2000; Zeitz et al., 2013; Zeitz et al., 2015; Zeitz et al.,
417 2005). All cCNSB genetic defects result in a defective ON-BC transmission. In contrast,
418 disruption of mainly the OFF-pathway caused by a mutation in the *Vsx1* gene did not
419 significantly alter refractive eye development or the susceptibility to experimentally induced
420 FDM (Chakraborty et al., 2014b). These findings lend further support to the selective
421 contribution of the ON-pathway to myopia at least in animal models. Recently it was shown
422 that *Vsx1* is expressed in both cone ON- and OFF-BCs, but not in rod ON-BCs (Shekhar et
423 al., 2016). We are not aware of studies showing myopia in mice with iCSNB, which affects
424 both ON- and OFF-BCs. However, in a recent study, patients with a variant near *GJD2* had
425 high myopia, supporting a potential role for altered signaling in cone-driven OFF pathways in
426 myopia development. Therefore, it is possible that multiple retinal pathways contribute to
427 myopia (Jiang et al., 2022).

428

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

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

451

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

453 **4.1. RNA-Seq studies in mouse models for cCSNB**

454 Several studies have identified novel myopia-associated candidate genes by whole
455 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*^{-/-}, *Lrit3*^{-/-} and *Grm6*^{-/-}) 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 ≤ 0.01 and an expression value of at least 5 transcripts per million reads
468 (TPM) from RNA-Seq data of adult *Gpr179*^{-/-}, *Lrit3*^{-/-} and *Grm6*^{-/-} 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*^{-/-}, *Lrit3*^{-/-} and *Grm6*^{-/-} 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

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

484 **4.2. Validation of RNA-Seq studies**

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

503

504 **4.3. Known genes implicated in CSNB**

505 Mutations in *NYX*, *GRM6*, *GPR179*, *TRPM1* and *LRIT3* that cause cCSNB affect protein
506 localization in retinal ON-BCs (Audo et al., 2012; Bech-Hansen et al., 2000; Dryja et al.,
507 2005; Li et al., 2009; Peachey et al., 2012; Pusch et al., 2000; van Genderen et al., 2009;
508 Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2005). The proteins localize in the outer plexiform
509 layer (OPL) and in most cases in the dendritic tips of ON-BCs (Zeitz et al., 2015). Similar to
510 human subjects, ON-BC function is affected in cCSNB mouse models (Gregg et al., 2003;
511 Koike et al., 2010; Masu et al., 1995; Morgans et al., 2009; Neuille et al., 2014; Peachey et
512 al., 2012; Zeitz et al., 2015). Proteins involved in cCSNB often show an interdependency in
513 their localization, and may or may not show correlated changes in expression levels (Neuille
514 et al., 2015). For example, nyctalopin (encoded by *Nyx*) and TRPM1 interact. Localization of
515 TRPM1 at the ON-BC dendritic tips is dependent on the presence of nyctalopin, mGluR6 and
516 LRIT3 (Cao et al., 2011; Hasan et al., 2020; Neuille et al., 2015; Pearing et al., 2011; Zeitz et
517 al., 2015). Using RNA-Seq, we showed that *Trpm1* mRNA levels are dependent on the
518 expression of *Gpr179*, *Lrit3*, and *Grm6*, and that expression levels of *Grm6* are dependent on
519 the expression of *Lrit3* (Figure 7). However, although *Trpm1* expression levels seems to be
520 dependent on *Gpr179* expression, the localization of TRPM1 at the dendritic tips of BCs does
521 not appear to be affected in *Gpr179*^{-/-} mice (Orhan et al., 2021; Orlandi et al., 2012). Aside
522 from the targeted gene in each knock-out strain, most of the other known genes underlying
523 cCSNB, are not strongly differentially expressed (Supplementary Tables S1 and S6),
524 suggesting that the 52 DEGs in the cCSNB mouse models are not necessarily candidate genes
525 for cCSNB.

526

527

528 **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

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

561 Strikingly, *Lect1* (*Cnmd*) was up-regulated in *Gpr179*^{-/-} and *Lrit3*^{-/-} mice and slightly down-
562 regulated in *Grm6*^{-/-} mice compared to wild-type mice. These findings were validated by RT-
563 qPCR (Figure 5B, cluster 2, Figure 6). In contrast, *Etv4* was down-regulated in *Gpr179*^{-/-} and
564 *Lrit3*^{-/-} mice and up-regulated in *Grm6*^{-/-} mice compared to wild-type animals (Figure 5B,
565 cluster 9).

566

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

577 photoreceptors, BCs, ACs and RGCs and that its expression appears to be reduced in
578 *Bhlhe23*^{-/-} mice (Woods et al., 2018).

579 **4.4.1. Single cell analyses of DEGs in subpopulation of bipolar cells**

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

586 **4.5. Pathway analyses of DEGs involved in CSNB and correlation with** 587 **myopia**

588 In rare cases, subjects with mutations in *NYX* (Yip et al., 2013; Zhang et al., 2007; Zhou et al.,
589 2015), *TRPM1* (Zhou et al., 2016) and *GRM6* (Jin et al., 2017; Xu et al., 2009) present with
590 early-onset high myopia despite the absence of documented cCSNB diagnosis. However, it is
591 believed that most mutations in *NYX*, *LRIT3*, *TRPM1*, *GRM6* and *GPR179* are not directly
592 responsible for high myopia. Instead, it is hypothesized that myopia in cCSNB is caused by a
593 disruption of the ON-pathway (Chakraborty et al., 2015). Our analysis revealed that **mitogen-**
594 **activated protein kinase (MAPK) pathways, synaptic signaling, G protein-coupled**
595 **receptor ligand binding pathways, and proteins implicated in eye, endoderm and**
596 **connective tissue development** were affected in cCSNB (Figure 10A). Some of the genes
597 appeared in multiple pathways (Figure 10B). In the following paragraphs we detail these
598 genes and pathways and describe correlations between cCSNB and associated ocular
599 alterations, focusing on myopia. When genes appeared in multiple pathways, they are
600 described only once. In addition, we focus on genes with additional data available in the
601 literature. These genes are highlighted in bold. A detailed description of all DEGs, their

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

605 **4.5.1. MAPK pathway**

606 To our knowledge, the MAPK signaling pathway has not previously been implicated in
607 cCSNB. In the normal retina, phosphorylated MAPKs are barely detectable. However,
608 subjects and mice lacking functional retinoschisin (RS1) exhibit decreased ERG b-wave
609 amplitudes and increased MAPK activation (Gehrig et al., 2007; Plossl et al., 2017). In
610 addition, under certain pathological conditions, such as induced retinal ischemia, MAPKs are
611 activated by phosphorylation in several retinal layers, including in the INL with a concomitant
612 reduction of the b-wave amplitude (Zeitze et al., 2015). Interestingly, **inhibitors of MAPK**
613 **phosphorylation** significantly normalized the b-wave amplitude after ischemia (Roth et al.,
614 2003). Although MAPK signaling in the retina has been investigated, its role in cCSNB and
615 accompanying ocular manifestations are poorly understood. Fifteen DEGs associated with the
616 MAPK pathway were identified: *Ackr3/Cxcr7*, *Bdnf*, *Cacna1s*, *Casp7*, *Ccnjl*, *Cdc25c*,
617 *Dusp4*, *Ldb2*, *Prkca*, *Ptprr*, *Spred3*, *Synj2*, *Tgfb2*, *Tpbp* and *Vgll4* (Figures 10 and 11).

618

619 **LRIT3** (MIM# 615004) encoding leucine-rich repeat, immunoglobulin-like, and
620 transmembrane domain-containing protein 3 (LRIT3) is mutated in human subjects with
621 cCSNB (MIM# 615058) and mice (Neuille et al., 2014). Interestingly, LRIT3 is itself a
622 modulator of the fibroblast **growth factor receptor 1** (FGFR1) (Kim et al., 2012), which also
623 plays an important role in the MAPK signaling pathway, though not identified as such in
624 pathway analyses. Phosphorylated FGFR1 regulates different signaling pathways including
625 **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

650 cells are well known (Afarid et al., 2016). Several polymorphisms in *BDNF* have been
651 associated with myopia (Musolf et al., 2017). In addition, *BDNF* appeared in the myopia
652 Harmonize GAD database (Rouillard et al., 2016) (Supplementary Table S6 and S7, Figure
653 8).

654

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

665

666 *CACNA1S* (MIM# 114208), coding for the L-type voltage-dependent calcium channel, alpha-
667 1S subunit, is required for normal skeletal and cardiac muscle function (Elbaz et al., 1995)).
668 *CACNA1S* is homologous to other calcium channel alpha-1 subunits, such as *CACNA1F*
669 (*Cav1.4*), which is mutated in subjects with incomplete CSNB (Bech-Hansen et al., 1998;
670 Strom et al., 1998). In the retina, *Cacna1s* was found to be expressed in BCs and more
671 recently in cones and rods (Supplementary Table S6, Figures 8-11). Initially, it was thought to
672 localize in dendritic tips of ON-BCs, similar to other genes implicated in cCSNB (Specht et
673 al., 2009; Tummala et al., 2014) but its exact protein localization in the retina remains

674 unclear, since commercially available CACNA1S antibodies have been shown to cross-react
675 with GPR179 (Hasan et al., 2016), which is localized at the dendritic tips of ON-BCs.
676 Calcium channels and their subunits in general have been linked to MAPK signaling (Ikeda,
677 2001) (Figure 11). L-type voltage-gated calcium channels in both retinal photoreceptors and
678 bipolar neurons are under **circadian control** (Hull et al., 2006; Ko et al., 2009; Ko et al.,
679 2007).

680

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

695

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

698 BCs (Supplementary Table S6 and S7, Figures 8-11). PTPRR has been implicated in MAPK
699 **deactivation** in the brain (for review (Chirivi et al., 2007)). Mice lacking *Ptprr* showed
700 increased phosphorylation of ERK1/2 in Purkinje cells and impaired motor coordination
701 (Chirivi et al., 2007). In the retina, PTPRR was suggested to play an important role in
702 neuronal development and maintenance of the mature retina (Horvat-Brocker et al., 2008).
703 Mutations in *PTPRR* could be involved in the development of **myopia** by a change in the
704 enzyme's ability to bind to, or dephosphorylate MAPK, leading to increased MAPK growth
705 signals. Increased expression of *PTPRR* in rapidly growing fetal retina and choroid may be
706 the result of normal developmental or growth regulation, suggesting that PTPRR plays a role
707 in controlling **ocular growth**. Disruption of this protein's function may account for the rapid
708 eye growth seen in highly myopic individuals during early childhood, which slows in
709 adulthood. As growth decreases, the need for this protein would be reduced (Hawthorne et al.,
710 2013). In addition, *PTPRR* was identified by **GWAS as linked to myopia** (Supplementary
711 Table S6 and S7).

712

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

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

724

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

730

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

746 (Supplementary Table S6, Figures 8-11). In tissues other than the retina, *DUSP4* was mainly
747 localized to the **nucleus** and found to be **induced** by multiple agents, including serum, growth
748 factors, UV-light, and oxidative stress. Depending on the tissue, it **dephosphorylates**
749 MAPKs, such as ERK, JNK or p38 (Figure 11). In addition, DUSP4 was shown to play a role
750 in innate and adaptive immunity, in cancer, and in brain function (Lawan et al., 2012;
751 Seternes et al., 2019). Supporting our RNA-Seq findings, a significant downregulation of
752 *Dusp4* expression was found in *Lrit3*^{-/-} and *Gpr179*^{-/-} mice by RT-qPCR and a trend was noted
753 in *Grm6*^{-/-} mice (Supplementary Figure 1). In *Trpm1*^{-/-} mice, significantly reduced expression
754 of *Dusp4* was also observed (Supplementary Figure 1). These findings were confirmed at the
755 protein level, but with more variability (Figure 12). Western blot analyses of retinal extracts
756 from wild-type mice revealed a band at 43 kDa, the calculated molecular weight of DUSP4.
757 This band was absent in *Dusp4*^{-/-} mice (data not shown). The role of DUSP4 in the retina is
758 largely unknown. Transcriptional profiling of endogenous germ layer precursor cells
759 identified *Dusp4* as an essential gene in zebrafish endoderm specification (Brown et al.,
760 2008). Although most of the vertebrate eye is derived from the ectoderm (Bassnett and Sikic,
761 2017), zebrafish *Dusp4* morphants had small necrotic heads, suggesting an essential role of
762 DUSP4 in anterior development (Brown et al., 2008). However, the role of DUSP4 in eye
763 development was not further described. Interestingly, in well-established models of refractive
764 error induction, *Dusp4* appeared to be down-regulated in the eye upon inductions of both
765 FDM and LIM in chicks and mice (McGlenn et al., 2007; Stone et al., 2011; Tkatchenko et al.,
766 2016). Subjects with an 8p deletion, which includes the 8p12 *DUSP4*, often present with eye
767 defects including nystagmus, strabismus and myopia, among other clinical syndromes
768 (<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.,
769 1987; Devriendt et al., 1999; Klopocki et al., 2006)). Such defects are also found in cCSNB
770

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

773

774 **4.5.2. Synapse**

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

784

785 ***GABRR1*** (MIM# 137161), coding for the gamma-aminobutyric acid receptor, rho-1
786 (***GABRR1***) (alternatively named GABA-C Receptor, rho-1 subunit), is a member of a family
787 of ligand-gated chloride channels that are the major inhibitory neurotransmitter receptors in
788 the central nervous system (Cutting et al., 1991). It represents one of the subunits of the
789 GABA-C receptor (rho1-rho3) (e.g. (Enz, 2001)) expressed in the inner retina in cone
790 photoreceptors, bipolar cells and horizontal cells (Supplementary Table S6, Figures 8 and 9).
791 In addition, ***GABRR1*** was found to be differentially expressed in bipolar cell-deficient
792 *Bhlhe23*^{-/-} mice (Woods et al., 2018). Mice deficient for the *Gabrr1* subunit lacked GABA-C
793 receptor-mediated GABA-evoked responses, and signaling from rod BCs to third order cells
794 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

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

821

822 *CA8* (MIM# 114815) and its mouse orthologue *Car8*, encoding carbonic anhydrase VIII
823 (CA8), has been found to be important for GABAergic synaptic transmission. *Car8* is mainly
824 expressed in the inner retina, with some expression in cone photoreceptors (Supplementary
825 Table S6, Figures 8 and 9). In addition, it was found to be differentially expressed in
826 *Bhlhe23*^{-/-} mice (Woods et al., 2018). *Car8* has been mostly studied in the brain, where it is
827 highly expressed in cerebellar Purkinje neurons (Jiao et al., 2005; Kato, 1990) and other parts
828 of the brain (Lakkis et al., 1997). Mice lacking functional *Car8* (Jiao et al., 2005) show gait
829 ataxia and dystonia with some ultrastructural differences in synapses between Purkinje cell
830 dendritic spines, indicating a role for carbonic anhydrase VIII in synapse formation and/or
831 maintenance. Similarly, subjects with mutations in *CA8* exhibit ataxia and mild mental
832 retardation (Turkmen et al., 2009). Recent studies in mouse retina showed CAR8
833 immunolabelling in rod BCs co-labelled for PRKCA, with particular bright staining in the
834 axon terminal regions and weaker staining in the cytoplasmic compartments (Puthussery et
835 al., 2011). In addition, some labelling was observed in a subset of cone BCs and GABAergic
836 ACs (Puthussery et al., 2011). Mice lacking *Car8* do not have a CSNB phenotype, as
837 measured by electroretinography, but light-evoked current responses from AII-ACs were
838 significantly larger and more prolonged than in control mice, suggesting that CAR8 is
839 important for modulating retinal neurotransmission (Puthussery et al., 2011). Interestingly,
840 genome-wide association studies found a potential association between *CA8* and myopia
841 (Kiefer et al., 2013) (Supplementary Table S6 and Figure 8). The reduced expression of *Car8*
842 in *Gpr179*^{-/-} and *Lrit3*^{-/-} mice, as identified by RNA-Seq studies, was confirmed by RT-qPCR
843 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*^{-/-}), 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*^{-/-} 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*^{-/-} 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

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

879

880 ***LRP2BP*** (MIM# 619020) encodes low density lipoprotein receptor-related protein 2b
881 (LRP2B). We are including it here among BC synaptic proteins because of its apparent retinal
882 localization (Woods et al., 2018) (Supplementary Table S6 and Figure 8). LRP2BP is a
883 scaffold protein, known to bind and recruit proteins to the megalin receptor (LRP2), which
884 participates in endocytosis and signal transduction (Petersen et al., 2003). Interestingly,
885 mutations in *LRP2* cause the Donnai-Barrow/Facio-Oculo-Acoustico-Renal syndrome, which
886 is partially characterized by high-grade myopia (Kantarci et al., 2007; Stora et al., 2009).
887 Histological investigations of ocular mouse tissues also identified a severe myopia phenotype
888 in megalin-deficient mice (Storm et al., 2014) and suggested that LRP2 is required for normal
889 eye growth (Cases et al., 2015). Similarly, a zebrafish model for *Lrp2* developed myopia
890 (Veth et al., 2011). Even more importantly, *LRP2BP* is located on chromosome 4q35.1, a
891 region deleted in cases with high myopia, among other disorders (Manolakos et al., 2013;
892 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 *Umodll* (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 *Umodll* remain unknown. *UMODL1* was found to be associated with

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

918

919 **4.5.4 Eye, endoderm, and connective tissue development**

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

927

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

936

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

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

951

952 ***EOMES*** (MIM# 604615) encodes eomesodermin (*EOMES*), also called *Tbr2*. It is directly
953 regulated by *Brn3b* and is important for RGC development (Mao et al., 2008). In agreement
954 with these observations, our gene expression data revealed that *Eomes* is mainly expressed in
955 the inner retina and more specifically, in RGCs (Supplementary Table S6 and Figure 8).
956 Homozygous silencing of *EOMES* leads to microcephaly with polymicrogyria and corpus
957 callosum agenesis (Baala et al., 2007). We are not aware of a retinal phenotype in subjects
958 with this gene defect; however, mice lacking *Eomes* (alias *Trpb2*) have reduced retinal
959 projections to non-image-forming brain nuclei and an attenuated pupillary light reflex
960 (Sweeney et al., 2014). Interestingly, subjects with CSNB have a reduced redilation and
961 smaller baseline pupil diameters, suggesting a disinhibition of intrinsically photosensitive
962 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*

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

989

990 **4.5.6 Other genes from myopia databases that are differentially regulated in at least one** 991 **mouse model with cCSNB**

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

995

996

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

998 Reduced expression of DEGs and their respective proteins in cCSNB may be due to reduced
999 expression levels or a lower number of cells expressing the DEGs. Genes implicated in
1000 cCSNB share a common phenotype, namely an ON-BC signaling defect. Although the
1001 morphology of the retina in human subjects and animal models with cCSNB is believed to be
1002 non-degenerative and stable, subtle cellular changes have been described in mice lacking
1003 *Lrit3* and *Trpm1* (Neuille et al., 2014; Takeuchi et al., 2018). SD-OCT revealed thinning of
1004 the INL, IPL, GCL, and nerve fiber layer in *Lrit3*^{-/-} mice (Neuille et al., 2014). This was not
1005 found in *Gpr179*^{-/-} mice (Orhan et al., 2021). Interestingly, rod BC terminals were
1006 significantly smaller in *Trpm1*^{-/-} retinas than in *Grm6*^{-/-} retinas, suggesting that deficiency of
1007 TRPM1, but not GRM6 affects rod BC synaptic terminal maturation and alter signaling
1008 between rod BCs and ACs (Kozuka et al., 2017).

1009 Notably, we found that *Prkca* transcripts were reduced in cCSNB retinas, and that, similar to
1010 TPBG, the level of PRKCA protein, which is specifically localized to rod BCs, was greatly
1011 reduced in *Gpr179*^{-/-} and *Lrit3*^{-/-} mice, but not in *Grm6*^{-/-} mice (Figure 13), while the numbers
1012 of nuclei present in the INL were unaffected (Figure 14). Visualizing synapses with a protein-
1013 independent marker needs to be performed to evaluate if the lower amounts of PRKCA and
1014 TPBG are due to morphological changes in rod BCs, particularly their synaptic terminals.
1015 Similarly, we found that levels of DA and DOPAC were also reduced in cCSNB retinas.
1016 Since the number of nuclei in the INL (Figure 14), remained unchanged in the cCSNB mouse
1017 models, and reduction of TH-positive dopaminergic amacrine cells was not significantly
1018 different in cCSNB compared to wild-type mice (tested for *Gpr179*^{-/-} versus *Gpr179*^{+/+})
1019 (Figure 15), we conclude that the reduced expression of some genes in cCSNB, as well as the
1020 reduction in DA and DOPAC levels are not due to degeneration of retinal cells, but may be
1021 linked to altered synapse morphology and/or lower RNA expression and/or reduced protein
1022 levels. We speculate that the absence of cCSNB genes such as *Gpr179* and *Lrit3*, leads to the
1023 classical ERG-defect but that other differentially regulated genes may contribute to myopia in
1024 those subjects with cCSNB. Similarly, exposure to reduced light levels in genetically
1025 unaffected individuals may also lead to lower expression of these genes and thus to myopia.

1026

1027 **6. Future perspectives**

1028 **6.1. Identification of differentially expressed genes in cCSNB models using a whole** 1029 **transcriptomic approach may yield novel proteins important for retinal signaling, as** 1030 **well as novel myopia-related genes**

1031 Mutations in *NYX*, *GRM6*, *GPR179*, *TRPM1* and *LRIT3* likely lead to cCSNB because the
1032 encoded proteins are necessary for ON-BC signaling (Audo et al., 2012; Bech-Hansen et al.,

1033 2000; Dryja et al., 2005; Li et al., 2009; Peachey et al., 2012; Pusch et al., 2000; van
1034 Genderen et al., 2009; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2005). The retina of cCSNB
1035 human subjects is generally well preserved and the disease course is non-progressive. The
1036 proteins are localized in the outer plexiform layer and, in most cases, in the dendritic tips of
1037 rod BCs and cone ON-BCs (Zeitz et al., 2015). Mouse models of cCSNB show a similar ON-
1038 BC transmission defect as human cases. The diagnosis is confirmed by an electronegative
1039 waveform at the full-field electroretinogram with severely reduced or absent b-wave under
1040 scotopic and photopic conditions, reflecting defective ON-pathway signaling (Zeitz et al.,
1041 2015). Candidate genes causing this disorder have been identified by linkage analyses in
1042 humans, using animal models, and more recently, by next-generation sequencing approaches
1043 (e.g.(Audo et al., 2012; Pusch et al., 2000; Varin, 2020; Zeitz et al., 2013; Zeitz et al., 2005)),
1044 with the help of transcriptomic data-bases to reinforce candidate genes (Zeitz et al., 2015).
1045 Recently, Woods et al. used comparative transcriptomic analyses in a mouse model lacking
1046 the rod BC transcription factor *Bhlhe23* (also known as BHLHB4 or basic helix-loop-helix
1047 family member, b4), to identify potential genes implicated in CSNB (Woods et al., 2018). The
1048 phenotype of *Bhlhe23*^{-/-} mice is slightly different than that of cCSNB. Although both
1049 phenotypes are stationary, rod BCs are almost completely absent in mice lacking *Bhlhe23*,
1050 resulting in a thinner INL but the cone pathway is not affected; thus *Bhlhe23*^{-/-} mice have an
1051 isolated rod BC defect, while both, rod BC and cone ON-BC functions are affected in
1052 cCSNB. This is also reflected by the b-wave amplitude only being affected under scotopic,
1053 but not photopic conditions in *Bhlhe23*^{-/-} mice (Bramblett et al., 2004). While the phenotype
1054 of *Bhlhe23*^{-/-} mice is different from cCSNB, night vision may indeed be affected. To date,
1055 however subjects with mutations in *BHLHE23* and a similar phenotype have not been
1056 described (Woods et al., 2018). This might be due to the fact that only scotopic vision is
1057 affected, and ERG recordings are required to detect such a phenotype in affected subjects.

1058 Because of the absence of rod BCs, one might expect that some of the genes differentially
1059 expressed in *Bhlhe23*^{-/-} mice may be important for night vision. However, expression of only
1060 a few of the “cCSNB-genes” was significantly reduced in *Bhlhe23*^{-/-} mice compared to wild-
1061 type mice. Furthermore, mice deficient for genes expressed at lower levels, such as mice
1062 lacking *Car8*, did not exhibit a typical cCSNB phenotype (Puthussery et al., 2011). This is
1063 consistent with our findings, indicating that while these approaches may identify novel
1064 candidates for cCSNB this is not necessarily the case.

1065 It is important to note that cCSNB is characterized not only by night blindness, but also by
1066 high myopia, nystagmus and often strabismus. Strikingly, since cCSNB is present from birth
1067 and young subjects are often not aware of their vision defects in dim light conditions, they are
1068 often first diagnosed due to their high myopia and/or infantile nystagmus. Thus, a main goal
1069 of this work was to identify other genes implicated in the same pathway as proteins
1070 underlying cCSNB and in that way identify additional candidates for the other associated
1071 ocular abnormalities associated with cCSNB. Since myopia represents one of the most
1072 common eye diseases worldwide, with increasing numbers of affected persons expected in
1073 coming years, we focused our study on DEGs implicated in cCSNB and associated with
1074 myopia.

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1078 **6.2. Retinal expression of DEGs, pathway analyses and correlation to eye phenotypes**

1079 To understand in which retinal cell types the 52 DEGs are expressed, we queried several
1080 retina expression databases, including single cell transcriptome databases, as well as PubMed

1081 (<https://pubmed.ncbi.nlm.nih.gov/>) and search tools such as “Google”
1082 (<https://www.google.com/>) (Macosko et al., 2015; Shekhar et al., 2016; Siegert et al., 2012;
1083 Siegert et al., 2009; Woods et al., 2018). These data showed that almost all 52 DEGs are
1084 expressed in the human retina, including in photoreceptors, BCs, ACs and RGCs, but for only
1085 a few of them was their retinal function described in the scientific literature (Supplementary
1086 Table S6 and Figure 8). Several DEGs, expressed in various retinal cell types were found to
1087 be associated with retinal disorders. For example, genes expressed in rods photoreceptors
1088 have been implicated in rod-cone dystrophies. Another example are genes expressed in ON-
1089 BCs, for which the encoded proteins are localized at the dendritic tips, which have been
1090 implicated in cCSNB (Zeitz et al., 2015). Variants in *FRMD7* (MIM # 300628), coding for
1091 Ferm domain-containing protein 7, which is expressed in ACs (Yonehara et al., 2016), are
1092 associated with idiopathic nystagmus in mice and human subjects (MIM #310700) (Tarpey et
1093 al., 2006). Thus, other genes expressed in ACs may also be linked to nystagmus. The
1094 contribution of genes expressed in **ACs** to **nystagmus** was further substantiated in a study
1095 with cCSNB humans and mice lacking functional nyctalopin (Winkelman et al., 2019). Thus,
1096 DEGs described herein and expressed in ACs may contribute to nystagmus observed in
1097 subjects with cCSNB (Figure 8). Recently, Bui Quoc and Milleret suggested that an abnormal
1098 routing of the **RGC** axons at the level of the optic chiasm might cause an imbalance between
1099 contra-lateral and ipsi-lateral projections and thus lead to **strabismus** (Bui Quoc and Milleret,
1100 2014). This might occur due to an abnormal expression of genes controlling **RGCs** axonal
1101 projections, and which may be differentially expressed in cCSNB. Further experiments and
1102 database analyses will be needed to determine if DEGs expressed in ACs and RGCs (Figure
1103 9) contribute to nystagmus and strabismus observed in human subjects with cCSNB. In
1104 addition, these genes may also represent candidate genes in cases of isolated nystagmus and
1105 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

1130 exposure to insufficient light levels, as found in children with not enough outdoor activities
1131 similarly leads to alterations of the ON pathway and myopia.

1132 Not surprisingly, the cCSNB DEGs included genes that are important for synapse formation
1133 and signaling. In addition, MAPK pathways and developmental genes were identified by our
1134 study, and to our knowledge, their association with cCSNB is novel. These same genes,
1135 however, are well known to be involved in the development of myopia (Li and Zhang, 2017),
1136 further reinforcing our predictions that genes differentially expressed in cCSNB are indeed
1137 good candidates for cCSNB-associated high myopia, as well as serving as candidates for non-
1138 syndromic myopia. Other DEGs identified here were not associated with specific myopia-
1139 related search terms or pathways, but, because of their expression in the retina and described
1140 physiological function, may be nevertheless be associated with myopia. Interestingly, a few
1141 DEGs have been implicated in circadian rhythms. Circadian clocks are cellular oscillators that
1142 generate daily rhythms even in the absence of external timing cues (Dunlap, 1999;
1143 Pittendrigh, 1993) and have also been associated with eye growth and refractive error
1144 development (Chakraborty et al., 2018).

1145

1146 **6.3 Novel candidate genes important for vision**

1147 The following DEGs represent genes not previously associated with myopia and may
1148 represent novel candidate genes underlying high myopia in cCSNB or other retinal disorders:
1149 *Adgra3/Gpr125, Afap111, Ampd3, Arc, **Cacna1s**, Ccnjl, Cdc25c, Dbhos, Eomes, Etv4,*
1150 *Fbox32, Frem3, Gm20754, Gm40477, Gm49760, Gm5478/Krt6c, **Gng4**, Insyn2b, Ldb2,*
1151 *Mast2, Mir670hg, Myh7b, Olfm3, Pdzph1, Plekhf1, **Prkca**, **Rgs16**, Shroom4, Spred3,*
1152 *St6galnac5, Synj2, Tac2, **Tpbp**, **Trpc1** and Umodl1.* More analyses are needed to validate
1153 their putative functional roles in vision. For a few of them, highlighted in bold, animal models

1154 or more functional analyses are available and may thus represent the best candidates to be
1155 analyzed in the future.

1156

1157 **6.4 Treatment of cCSNB and myopia**

1158 Although cCSNB is believed to be a relatively mild non-degenerative stationary retinal
1159 disease, this study shows that gene defects causing cCSNB impact the expression of other
1160 genes important for the correct development of the retina and eye. Treatment efficacy may
1161 also be impacted. Indeed, at least in mice, cCSNB treatment was more successful in immature
1162 retina, and only under scotopic conditions (Hasan et al., 2019; Scalabrino et al., 2015; Varin
1163 et al., 2021a; Varin et al., 2021b), suggesting that the development of the retinal structure,
1164 e.g., synapse formation, is irreversibly impaired in cCSNB. These subtle changes of the retina
1165 may only be visible with sensitive methods such as immunohistochemistry or electron
1166 microscopy. Such developmental defects may be regulated by the genes differentially
1167 expressed in cCSNB identified in this study. Replacing the missing gene implicated in
1168 cCSNB, such as *GRM6* or *LRIT3*, by an AAV-approach may restore the correct localization
1169 of the corresponding protein and its function, but it is not clear if this will also restore the
1170 normal expression of the cCSNB-associated DEGs. Defects in developmental processes, such
1171 as synapse formation, may lead to the observed failure to rescue photopic vision in adult mice.
1172 Furthermore, whether an AAV-based therapeutic approach can cure myopia remains unclear.
1173 Although refractive errors associated with myopia can be corrected using optical correction,
1174 myopic subjects may still develop a number of other vision-threatening complications such as
1175 myopic macular degeneration, retinal tears, retinal detachment and glaucoma (Hornbeak and
1176 Young, 2009). Therefore, identifying therapeutic approaches to prevent the development of
1177 myopia would be beneficial. Pharmacological treatments may become important means to

1178 prevent and/or slow the progression of myopia, but they are unlikely to be able to revert or
1179 cure established myopia.

1180

1181 **6.4.1 Pharmacological myopia treatment**

1182 A signaling cascade, which begins in the retina, via photoreceptors, BCs and dopaminergic,
1183 GABAergic, and glycinergic ACs, and propagate across all ocular tissues to the sclera is
1184 likely to contribute to human myopia development and progression (reviewed by (Tkatchenko
1185 and Tkatchenko, 2019)). This signaling cascade is triggered by optical blur, which plays a
1186 critical role in this process. Here, we suggest that cCSNB is an additional valuable model to
1187 study myopia, because the disruption of inner retinal signaling in cCSNB has a significant
1188 impact on refractive eye development, potentially similar to a low light environment. As
1189 discussed above, the neurotransmitter **DA and its metabolite DOPAC** have been proposed to
1190 regulate refractive eye development and their retinal concentrations are reduced in myopia
1191 models (Chakraborty et al., 2015; Pardue et al., 2008; Stone et al., 1989; Zhou et al., 2017).
1192 Here, we have shown that DA and DOPAC levels are also reduced in the retina of cCSNB
1193 mice. **Intravitreal injections** of **DA** in rabbits (Gao et al., 2006) and **intraperitoneal**
1194 **injections** of DA in guinea pigs (Mao et al., 2010) and mice (Landis et al., 2020) inhibit FDM
1195 myopia induction. Enhancing DA signaling by daily intraperitoneal injections of non-selective
1196 **DA receptor agonists** prevented FDM in chicken, guinea pig, monkey and mice (reviewed by
1197 (Zhou et al., 2017). More studies are needed, however, to define the cellular mechanisms of
1198 DA action, a requirement for the development of an effective myopia treatment. **Bright light**
1199 has also been shown to protect against the development of myopia and to increase DA release
1200 in a number of studies with **animal models and in children** (reviewed by (Zhou et al., 2017).
1201 It has been suggested that retinal DA **may induce choroidal thickening and inhibit ocular**

1202 **growth** by triggering the release of other transmitters such as **nitric oxide (NO)** from the
1203 retina or choroid (reviewed by (Zhou et al., 2017). **Clinical trials** testing the use of
1204 **dopaminergic agents** to treat amblyopia, myopia and attention deficit disorders revealed
1205 **negative side effects of systemic activation of DA** signaling (reviewed by (Zhou et al.,
1206 2017)). In contrast, local delivery of DA by APO eye drops given to infant rhesus monkeys
1207 reduced development of FDM in the absence of systemic toxicity and other negative side
1208 effects (Iuvone et al., 1991). Despite these promising findings, we are not aware of further
1209 studies in non-human primates or clinical trials using dopaminergic compounds to inhibit
1210 myopia progression.

1211 A few other pharmacological agents targeting neurotransmitter receptors have been shown to
1212 suppress the development of experimental myopia in animals, such as the **muscarinic**
1213 **acetylcholine receptor (mAChR) antagonists** pirenzepine and atropine, which are expected
1214 to act on muscarinic receptors, expressed in the sclera and in the inner retina. Further long-
1215 term clinical studies with large samples sizes are needed to validate the efficacy of this
1216 potential anti-myopia therapy (reviewed (Tkatchenko and Tkatchenko, 2019; Wang et al.,
1217 2021)). Today, however, **atropine**, a **nonselective muscarinic receptor antagonist**, is the
1218 most widely used anti-myopia drug, although the exact mechanism of atropine's inhibitory
1219 effect on myopia is not well understood. Several clinical trials using atropine eye drops in
1220 combination with optical devices such as multifocal lenses that impose a peripheral positive
1221 defocus, showed positive outcomes, albeit with low efficacy (reviewed (Tkatchenko and
1222 Tkatchenko, 2019)). It would be interesting to investigate if atropine, potentially together with
1223 optical devices would also inhibit myopia development in CSNB patients and animal models.

1224 The recent identification of **signaling pathways**, identified by us here and others (Tkatchenko
1225 and Tkatchenko, 2019)), that control the response of the eye to optical defocus and
1226 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

1252 myopia model, refractive errors are only measured following experimental myopia inductions.
1253 Alternatively, treatment efficacy could be evaluated by measuring the restoration of
1254 neurotransmitter and other metabolite levels or by experimentally assessing the normalization
1255 of gene expression within the gene regulatory networks involved in myopia development.
1256 Together, we and others showed that myopia is a complex disorder influenced by many
1257 genetic and environmental factors. Future studies are needed to develop therapies targeting
1258 these signaling cascades and determine the efficacy of potential treatment approaches
1259 (Brennan et al., 2021).

1260

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1262

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11

12 **Figures legends:**

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

20

21 **Figure 2:** Example of scotopic electroretinograms in mice lacking *Aplp2*, a gene associated
22 with myopia in humans. Lack of *Aplp2* causes a dose-dependent decrease in the b-wave
23 amplitude (A). The b-wave implicit time was increased in mice lacking *Aplp2*. Lack of *Aplp2*
24 did not have a significant impact on either a-wave amplitude or a-wave implicit time. Lack of
25 *Aplp2* caused a decrease in amplitude and an increase of the implicit time of the oscillatory
26 potentials (B). Figure was taken from Tkatchenko *et al.*, 2015 (Tkatchenko *et al.*, 2015) with
27 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 **Figure 6:** Examples of genes found to be differentially expressed in three (red) and two
3 (green) cCSNB mouse lines by RNA-Seq studies and validated by RT-qPCR experiments.
4 Green boxes indicate the genes differentially expressed in two cCSNB mouse lines. Some
5 genes appeared to be significantly differentially expressed only in two cCSNB mouse lines by
6 RNA-Seq investigations, but were significantly differentially expressed in all three mouse
7 lines by RT-qPCR studies (e.g. *Prkca* and *Tpbp*). Other genes appeared to be significantly
8 differentially expressed in three cCSNB mouse lines by RNA-Seq investigations, but were
9 statistically significantly differentially expressed only in two mouse lines by RT-qPCR
10 studies (e.g. *Frem3* and *Ptprp*). Data were tested for normality and analyzed using the
11 nonparametric Mann-Whitney test to compare expression. Values are reported as standard
12 deviations. Statistical significance was obtained with p-values, where $p \leq 0.05$ =* and $p \leq 0.01$
13 = **. NRQ = Normalized relative quantity.

14

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

19

20 **Figure 8:** Schematic drawing (created with BioRender.com) of differentially expressed genes
21 (DEGs), localization of their expression in the retina and their association with myopia. Genes
22 in the white box, also appeared in myopia databases and were found to be differentially
23 expressed in at least one cCSNB mouse line. They show expression in the retina although in
24 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*^{-/-}, *Lrit3*^{-/-} and
16 *Grm6*^{-/-} 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 ≤ 0.05 = * and p ≤ 0.01 = **.

20

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

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

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

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9 **Figure 15:** Quantification of all TH-positive cells revealed no significant differences between
10 *Gpr179*^{+/+} and *Gpr179*^{-/-} (n=4 mice).

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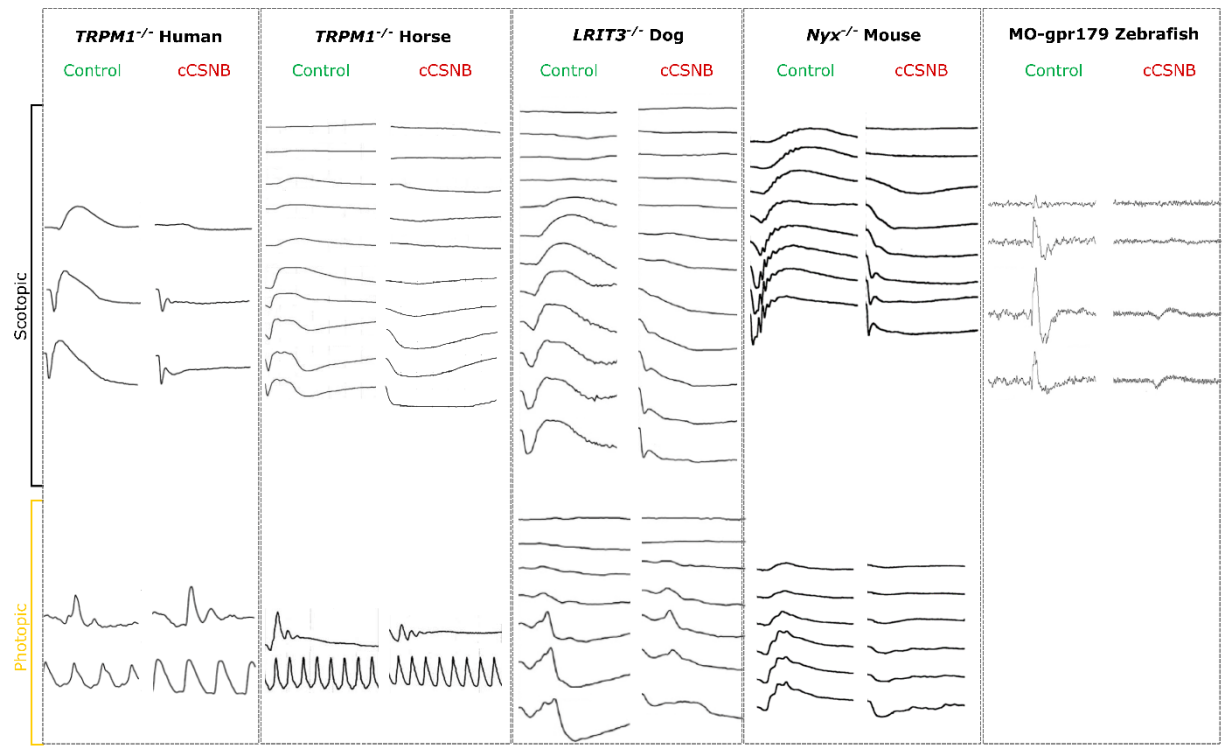
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2 **Figure 1**

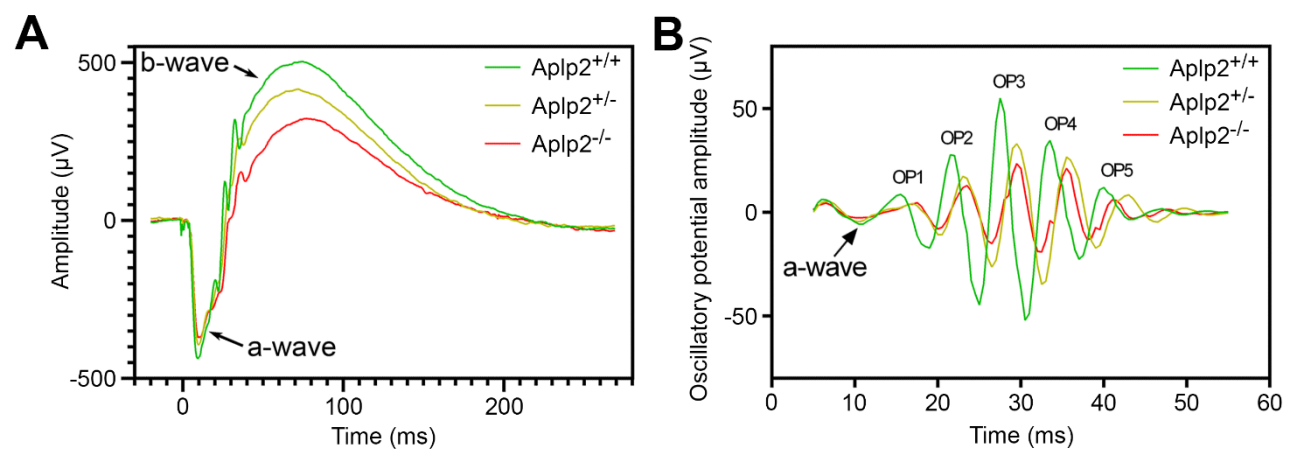


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6 **Figure 2**

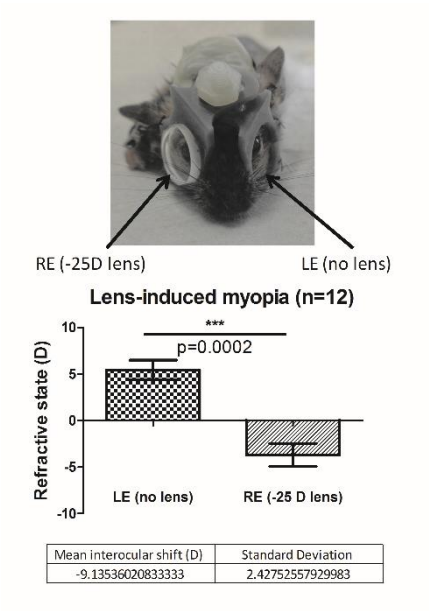


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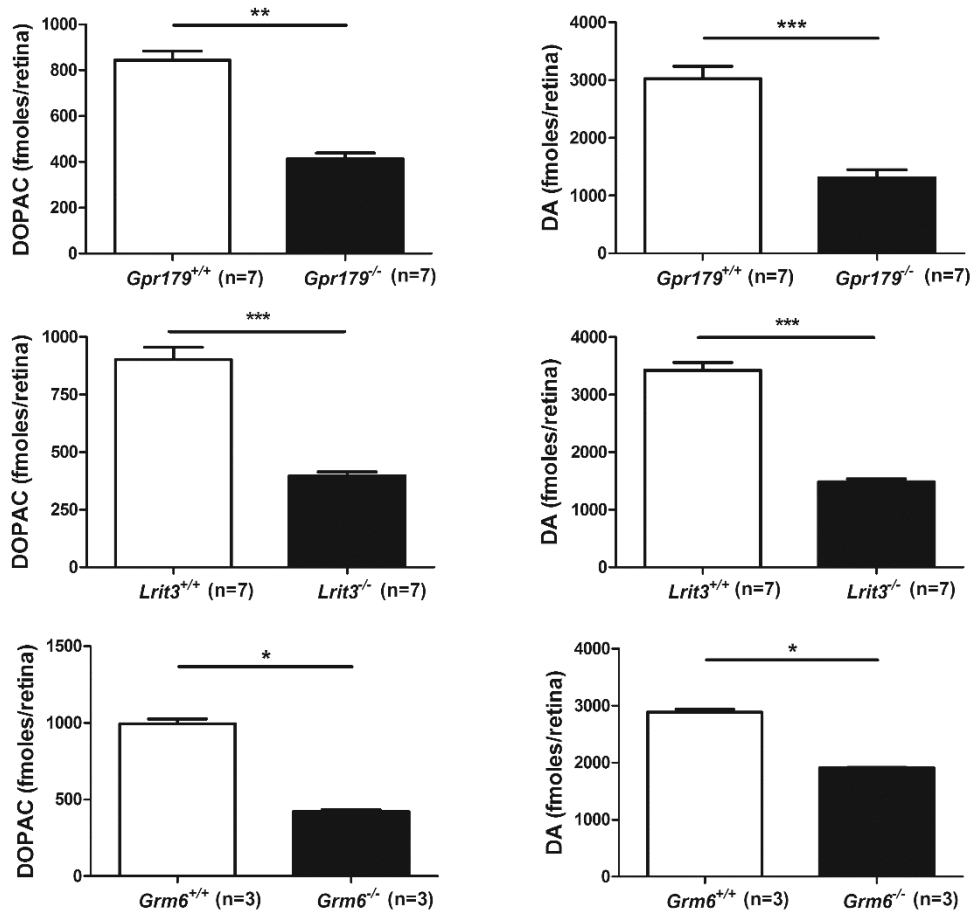
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2 **Figure 3**



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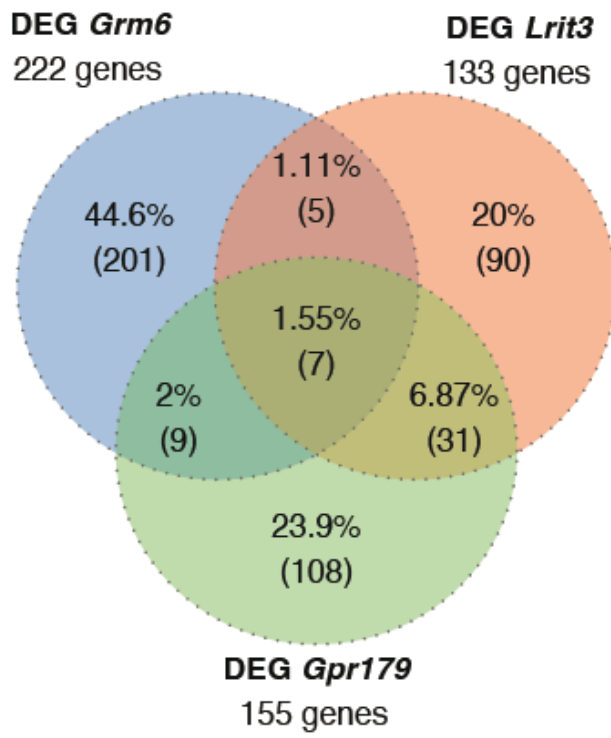
4 **Figure 4**



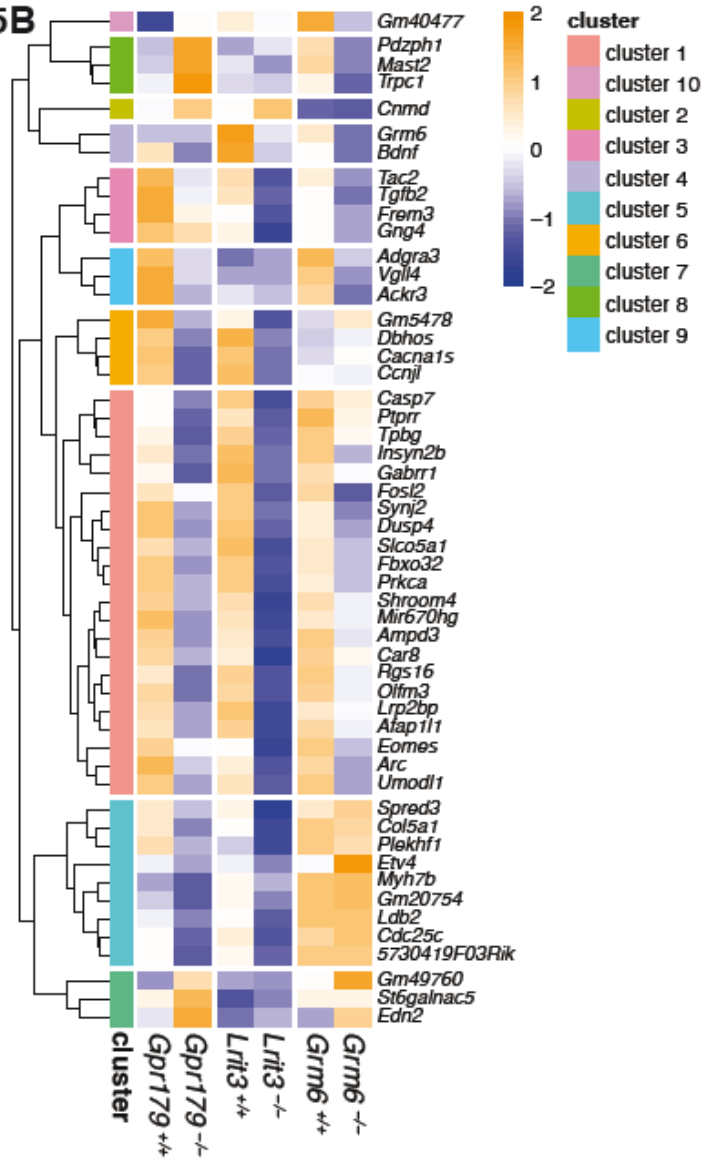
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2 **Figure 5**

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5B



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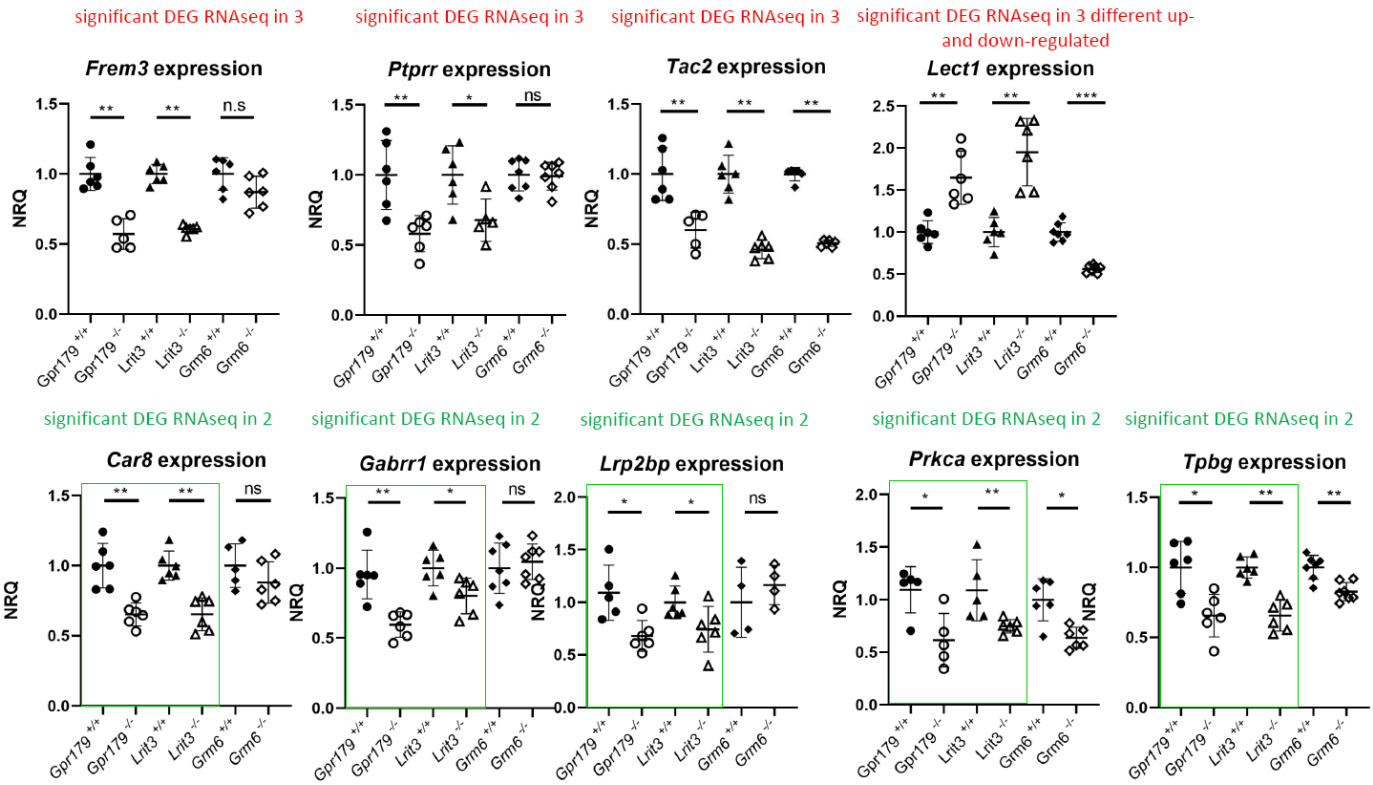
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7 **Figure 6**

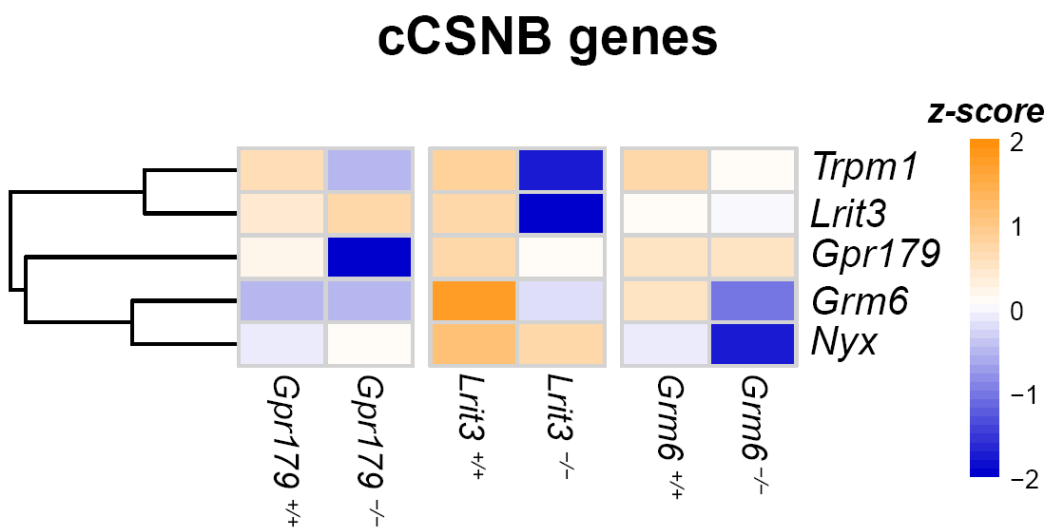
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4 **Figure 7**

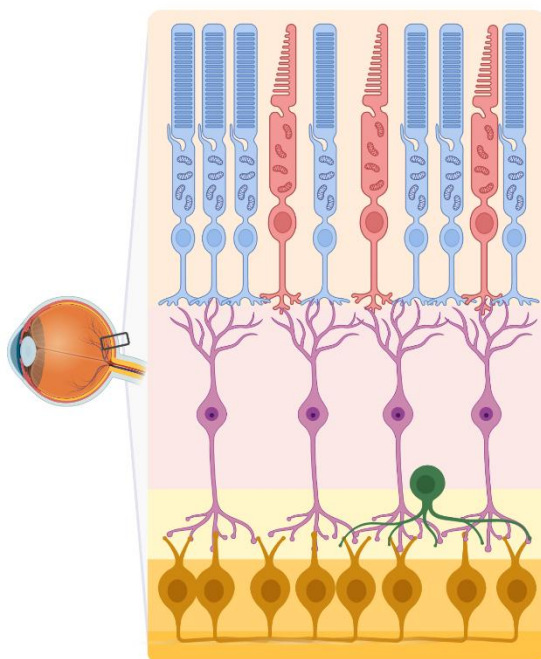


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6 **Figure 8**

The eye with focus on the retina

Different retina cell types



DEGs in cCSNB

ADGRA3, AFAP1L1, CACNA1S, CHRM1, COL1A1, COL22A1, COL5A1, GNG4, LECT1, MAST2, TGFB2, TRPC1, VGLL4

ADGRA3, CACNA1S, CAR8, CASP7, CHRM1, CNTN4, COL1A1, COL22A1, CXCR7, GABRR1, GNG4, KCNMA1, LECT1, MAST2, PTPRR, SPRED3, TAC2, TGFB2, TPBG, TRPC1

ADGRA3, AFAP1L1, AMPD3, BDNF, CACNA1S, CAR8, CASP7, CCNJL, CDC25C, CHRM1, CNTN4, COL1A1, COL22A1, COL5A1, CXCR7, DUSP4, EDN2, ETV4, GABRR1, GNG4, GRM6, KCNMA1, LDB2, LECT1, LRP2BP, MAST2, NTRK2, PLEKHF1, PRKCA, PTPRR, RGS16, SLC05A1, SPRED3, ST6GALNAC5, SYNJ2, TAC2, TGFB2, TPBG

ARC, BMP6, CAR8, CHRM1, CNTN4, COL1A1, COL22A1, CXCR7, FBXO32, GABRR1, GNG4, KCNMA1, LDB2, LECT1, NTRK2, OLFM3, PLEKHF1, PTPN5, PTPRR, TAC2, TGFB2, TPBG, VGLL4

BDNF, CAR8, CHRM1, CNTN4, CXCR7, EOMES, FOSL2, FREM3, GABRR1, GNG4, KCNMA1, LECT1, NTRK2, PLEKHF1, PRPH, PTPRR, TGFB2, TPBG, TRPC1, VGLL4

DEGs in cCSNB and associated with myopia

CHRM1, COL1A1, COL22A1, COL5A1, TGFB2, VGLL4

CAR8, CASP7, CHRM1, CNTN4, COL1A1, COL22A1, CXCR7, GABRR1, KCNMA1, PTPRR, TGFB2

BDNF, CAR8, CASP7, CHRM1, CNTN4, COL1A1, COL22A1, COL5A1, CXCR7, DUSP4, EDN2, GABRR1, GRM6, KCNMA1, LRP2BP, NTRK2, PTPRR, SLC05A1, TGFB2

BMP6, CAR8, CHRM1, CNTN4, COL1A1, COL22A1, CXCR7, GABRR1, KCNMA1, NTRK2, OLFM3, PTPN5, PTPRR, TGFB2, VGLL4

BDNF, CAR8, CHRM1, CNTN4, CXCR7, FOSL2, GABRR1, KCNMA1, NTRK2, PRPH, PTPRR, TGFB2, VGLL4

Rods

Cones

Bipolar Cells

Amacrine Cells

Ganglion Cells

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

FAM13A, MN1, PRSS56, TSHR, UMODL1

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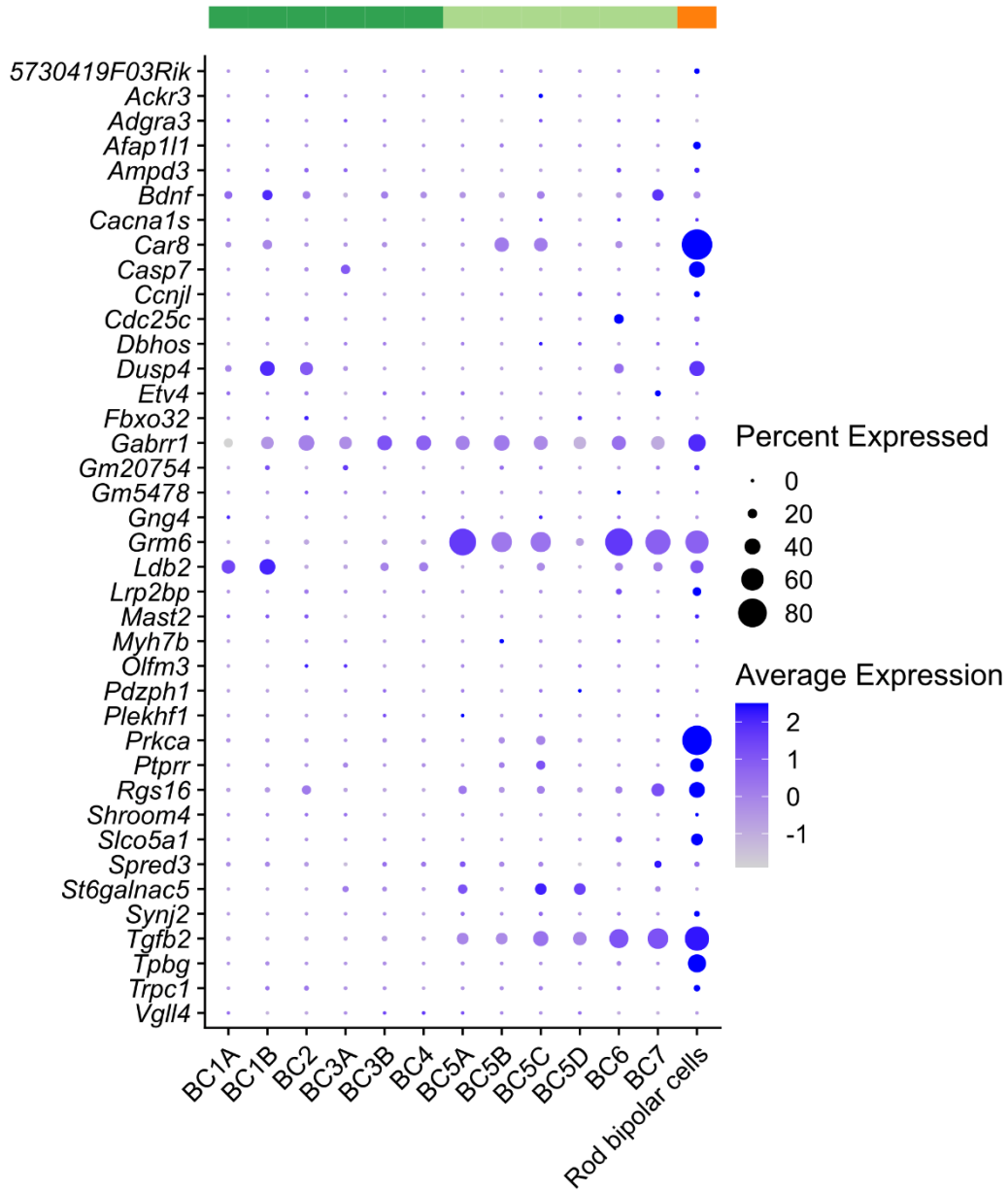
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10 **Figure 9**

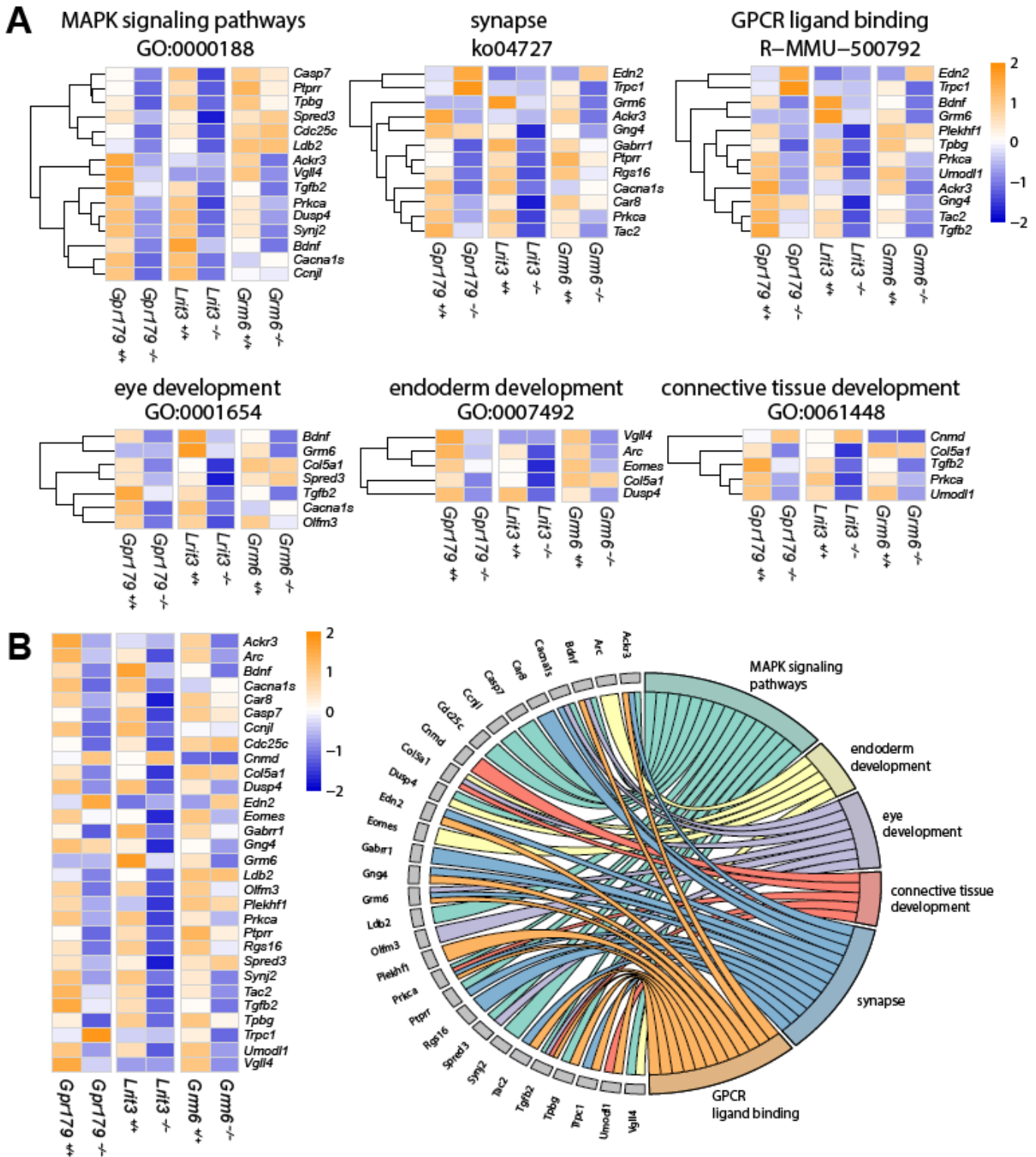
Cell type ■ Cone OFF BCs ■ Cone ON BCs ■ Rod BCs



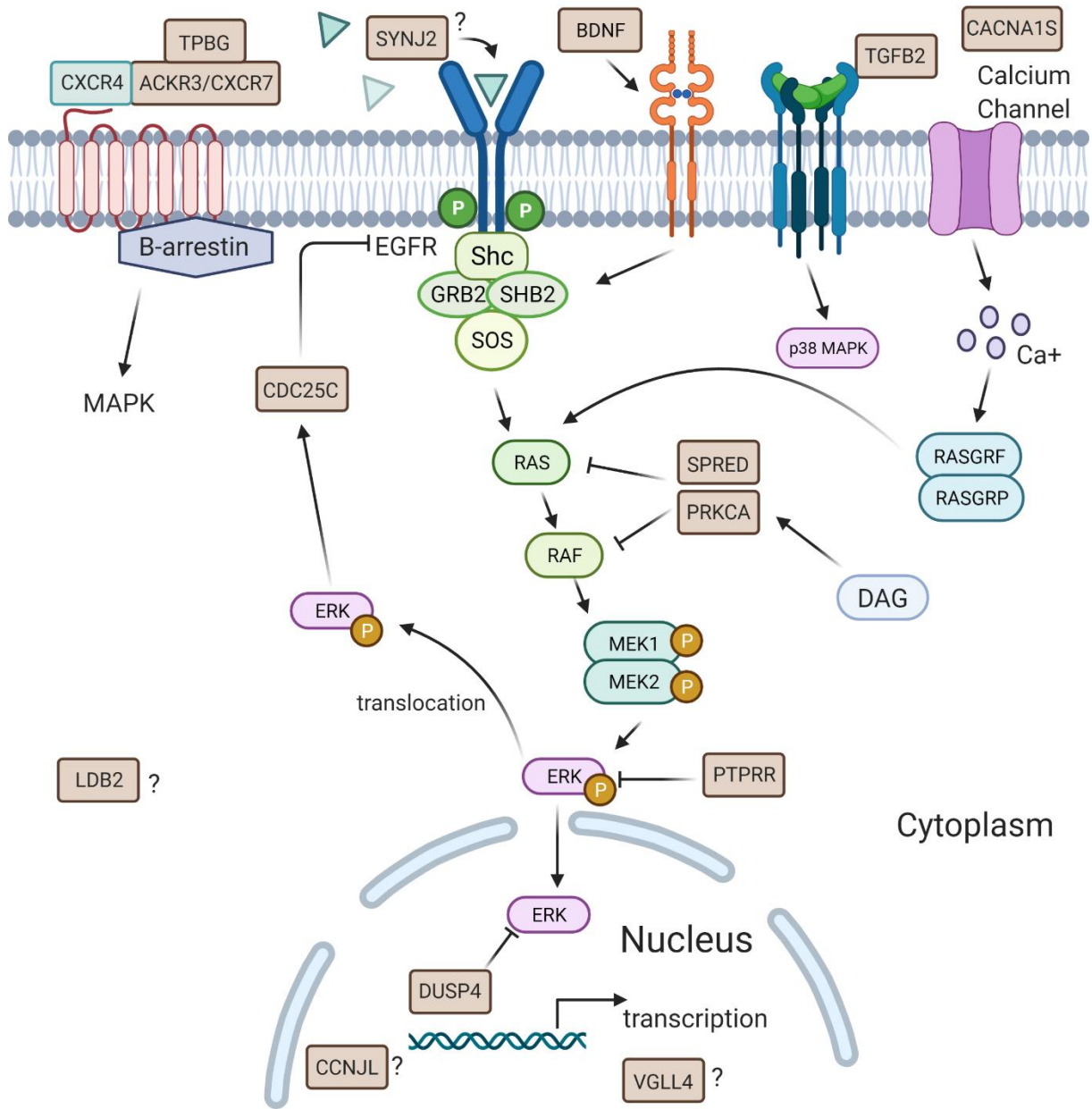
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3 **Figure 10**



1 Figure 11



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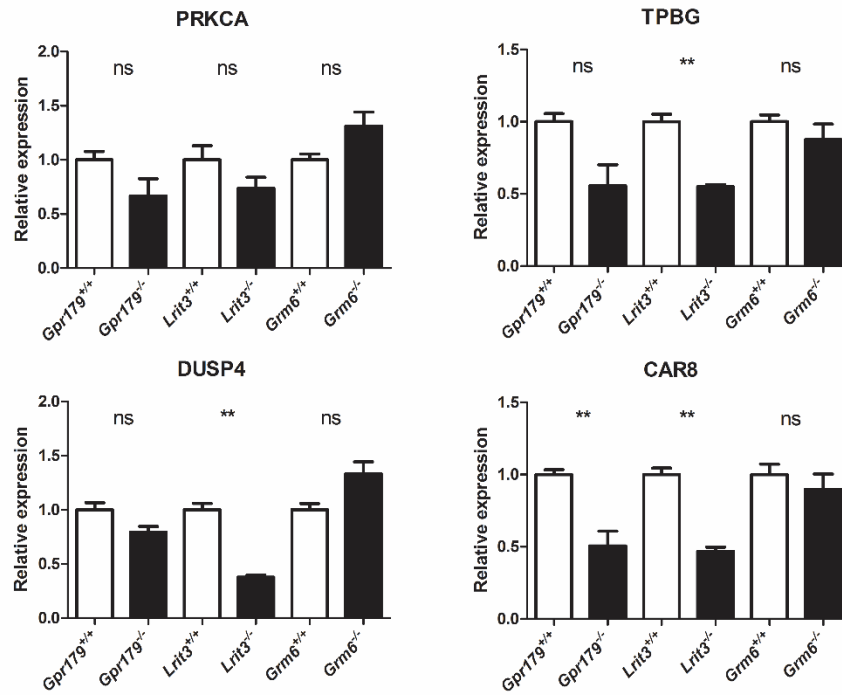
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1 **Figure 12**



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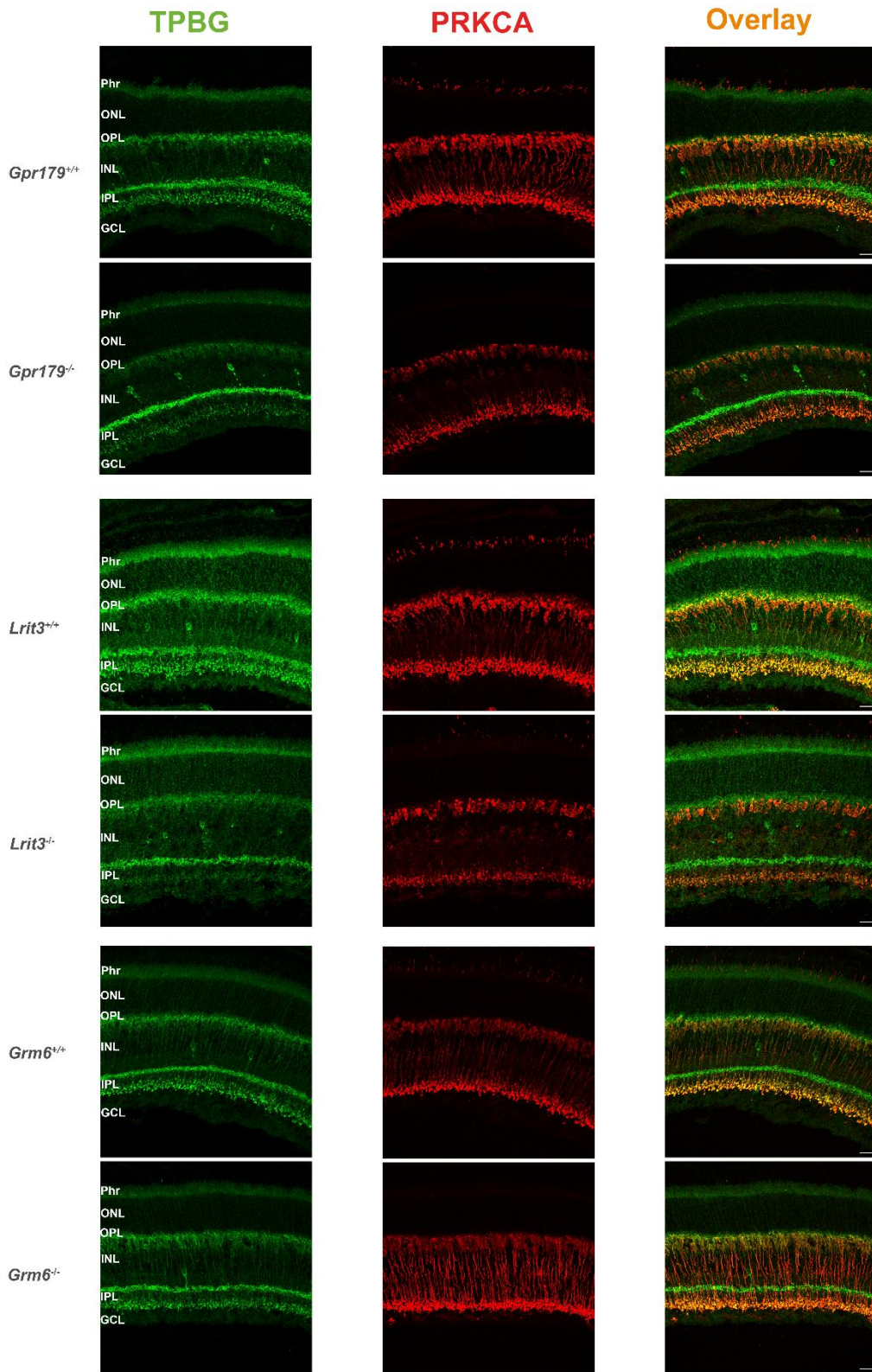
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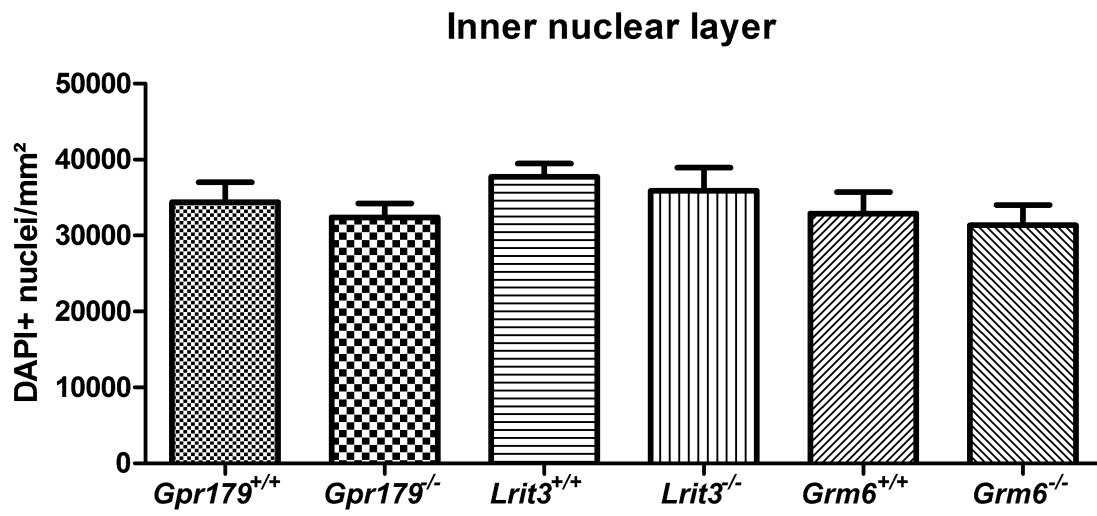
1 **Figure 13**



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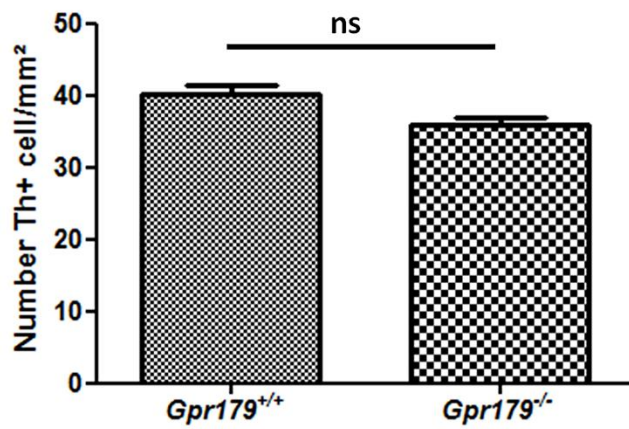
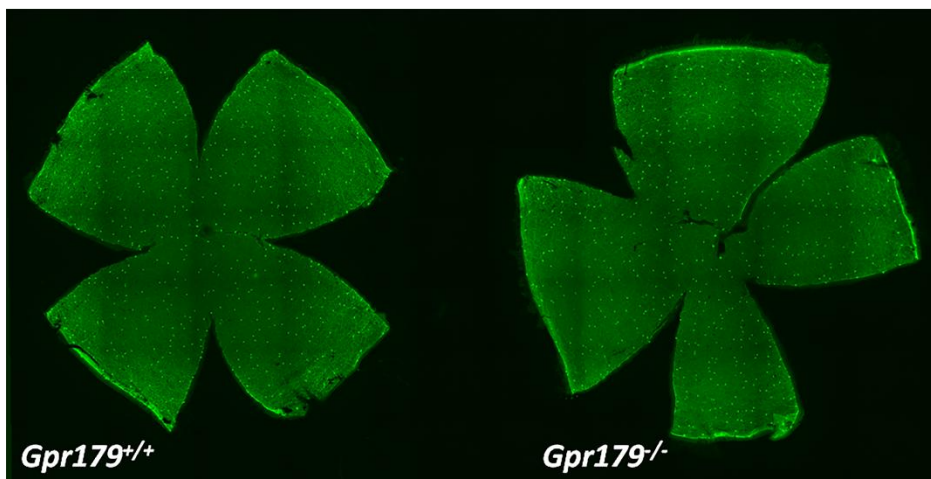
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1 Figure 14



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3 Figure 15



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