Natural Course of Refractive Error in Congenital Stationary Night Blindness: Implications for Myopia Treatment

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Purpose. A range of pharmacological and optical therapies are being studied and implemented in children with myopia to reduce the progression of myopia. At present, the efficacy of these myopia reduction treatments in children with underlying inherited retinal disorders (IRDs) is largely unknown. To evaluate this efficacy, it is essential to first understand the natural progression of myopia within each distinct underlying IRD. We investigated the natural course of refractive error throughout childhood in patients with congenital stationary night blindness (CSNB) of the Schubert-Bornschein type.

Methods. We retrospectively assessed a total of 295 refraction measurements in 127 patients with CSNB (48 with "complete" CSNB [CSNB1] and 79 with "incomplete" CSNB [CSNB2]) at different ages between 0 and 21 years old. None had a history of myopia control treatment. A linear mixed effects model was fitted on the data to analyze the natural course of refraction in these patients.

Results. The fitted model showed that refractive error in patients with CSNB increases quickly toward myopia in the first years of life. After the age of 4 years, there was a minimal progression of only −0.12 diopters (D) per year up to 15 years, after which the refraction seemed stable. All (43/43) of the patients with CSNB1 aged > 4 years were myopic and 84% (62/74) of the patients with CSNB2 aged > 4 years were myopic at the last refraction measurement.

Conclusions. In general, the refractive error of children with CSNB changes minimally after the age of 4 years old. A critical approach to myopia control interventions in these children is warranted.

Keywords: congenital stationary night blindness (CSNB), refractive course, myopia

Children with high myopia face an increased risk of developing vision-compromising conditions later in life, such as myopic macular degeneration and retinal detachment.[1–3] Although myopia usually manifests during their school years, a small subset of children already exhibit high levels of myopia very early in life. Limited research has been conducted in these young children with high myopia.[4–6] However, the available data suggest differences in the course of refraction in this pre-school age group compared to what is generally observed in school-aged children with myopia.[4–6] These differences are probably due to different underlying etiologies of myopia in the very young, including prematurity and inherited retinal disorders (IRDs), as opposed to a multifactorial origin in school-aged children.[4,7,8]

The Schubert-Bornschein type of congenital stationary night blindness (CSNB) is an IRD caused by defective signal transmission between photoreceptors and bipolar cells.[9] This defective signal transmission results in an electronegative bright flash electroretinogram (ERG).[10,11] CSNB type 1 (CSNB1; "complete" CSNB) is characterized by dysfunction in the ON bipolar pathway, whereas CSNB type 2 (CSNB2; "incomplete" CSNB) is characterized by dysfunction in both the ON and OFF bipolar pathways. Several genes are associated with CSNB1, with either X-linked or autosomal recessive inheritance, whereas the great majority of patients with CSNB2 have pathogenic variants in just one gene (*CACNA1F*), with X-linked inheritance.[10]

The majority of both patients with CSNB1 and patients with CSNB2 are myopic, with patients with CSNB1 typically exhibiting more severe myopia than those with CSNB2. Whereas hyperopia is extremely rare in CSNB1, the range of refractive errors in CSNB2 includes both high myopia and hyperopia.[9,10] Although the mechanism of the association between myopia and CSNB is not exactly known, it is suggested that disruption of the ON pathway contributes to the development of myopia.[12,13]

A range of pharmacological and optical therapies are being studied and implemented in children with myopia to reduce the progression of myopia.[14–17] The ultimate goal of these treatments is to preserve good visual acuity throughout one's life by reducing complications related to high myopia.[2] Although this objective is debatable in children with progressive IRDs where visual acuity may already be

severely compromised before complications due to high myopia become relevant, it holds particular significance for those who develop high myopia early in life due to underlying nonprogressive conditions such as CSNB. At present, the efficacy of myopia reduction treatments in children with underlying IRDs is largely unknown.[18] To evaluate this efficacy, it is essential to first understand the natural progression of myopia within each distinct underlying IRD.

A limited number of studies is available on the development of refractive errors in children with IRDs, and most of these were performed in small cohorts.[19–22] Hendriks et al. reported on refractive errors in a large group of patients with various IRDs, but this study was hampered by small subgroup analyses per distinct IRD and did not have longitudinal data available.[23] A very recent study of Igelman et al. examined the natural history of myopic progression in children with CACNA1F, NYX, and TRPM1 genotypes.[22]

At Bartiméus Diagnostic Center for Complex Visual Disorders, we assembled a large cohort of patients with CSNB1 and CSNB2. In this large group of patients with CNSB, we set out to investigate the natural course of refractive error throughout childhood.

Methods

Study Population

For this study, we included 87 of the 101 patients with CSNB from the 2013 study by Bijveld et al.,[10] and an additional 47 patients examined at our clinic over the last years. We included patients who showed clear phenotypic characteristics (including a pathognomonic ERG for CSNB1 or CSNB2) along with genotypic traits linked to CSNB.[10] Additional inclusion criteria were the availability of refraction data and no history of any myopia control treatment. In four patients with *TRPM1* mutations, only one heterozygous mutation was identified. However, because these patients exhibited an evident CSNB phenotype (including a pathognomonic ERG) we included them in our study. Patients with *CABP4* mutations were excluded. In the past, *CABP4* mutations have been described as a cause of autosomal recessive CSNB2. However, because these patients have a different phenotype, including photophobia, absence of night blindness, and mainly hyperopia, *CABP4* mutations are now regarded as a cause of cone-rod synaptic disorder but not as a form of CSNB.[24] Most of the available data were obtained during childhood (see Supplementary Fig. S1), and because myopization due to growth of the eye is most likely to stabilize before the age of 21 years,[25] we also excluded 14 datapoints (7 patients) at an age > 21 years. Furthermore, we excluded one (the first) measurement of a 5-year-old patient with CSNB1 with *GRM6* mutations, because the patient's myopia showed an unlikely change of approximately 3.5 diopters (D) for both eyes in 5 months' time (from −9.5 D to −6 D). This resulted in a total of 295 refraction measurements in 127 patients with CSNB (48 with CSNB1 and 79 with CSNB2) at various ages during childhood. The distribution in genes, male–female ratio, and mean age at first visit of these patients are shown in Table 1. An overview of the genetic mutations found in our study group is presented in Supplementary Table S1.

All investigations were conducted in accordance with the principles of the Declaration of Helsinki and written informed consent was obtained from all patients.

Refraction Data

Of the 295 refraction measurements, 192 were obtained from the prescription of current glasses, 90 by cycloplegic retinoscopy, 6 from cycloplegic autorefraction measurements, 5 from contact lens prescriptions (which were converted to an eyeglass prescription), and 2 were of unknown origin. If only a non-cycloplegic autorefraction measurement was performed at a consultation, this was not included in the data to avoid instrument myopia artifacts. Of the 127 patients, 39 had only 1 refraction measurement. The remaining patients had an average of 2.9 measurements.

We used the average spherical equivalent of the two eyes as the outcome measure in the analyses, after verifying that only minor differences in refraction between both eyes of the patients existed and that there was no statistically significant increase or decrease in anisometropia as a function of age.

Statistical Analyses

To analyze the natural course of refraction in patients with CSNB, a linear mixed effects model was fitted to the data. The model initially included restricted cubic splines with multiple knots to evaluate the general trend of the data. Because this basically showed that the natural course of the refraction can be modeled by three approximately linear branches, we replaced the restricted cubic splines with linear splines with two knots. Based on the literature,[10] genotype was considered a covariate and was therefore included as a fixed effect in the model. To account for individual variation in each patient, the intercept as well as the slope was included as a random effect in the model. After verifying that the slope hardly contributed to the random effect, it was discarded from the model to reduce the degrees of free-

Table 1. Distribution of the Affected Genes, Male/Female Ratio, Mean Age at First Visit of the Study Population, and Mean Follow-Up Time for Those Patients With Multiple Measurements

CSNB Type	Gene	Number of Patients	M : F	Mean Age at First Visit, Y	Number of Patients With Follow-Up	Mean Follow-Up Time, Y
1	*GPR179*	3	2 : 1	12.1	1	1.2
1	*GRM6*	4	2 : 2	6.0	2	3.1
1	*NYX*	29	29 : 0	6.4	16	4.0
1	*TRPM1*	12	3 : 9	7.3	9	2.8
2	*CACNA1F*	79	79 : 0	6.3	60	4.8
	Total	127	115 : 12	6.5	88	4.4

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dom and therefore allow also smaller subsets of data to be analyzed. The final coefficients were determined using the restricted maximum likelihood method and the significance of parameters was assessed using confidence intervals. The assumptions of a mixed effects model – normally distributed residuals and homogenic variances – were evaluated visually. To determine if the refraction of patients with CSNB1 is statistically different from patients with CSNB2, a Mann-Whitney-Wilcoxon rank test was used. Statistical significance was assumed at $P < 0.05$ or a non-overlap of the 83% confidence intervals ($z = 1.39$).[26] The software used was R, version 4.3.1, with packages readxl, lme4, rms, lspline, effects, and ggplot2.

Results

Anisometropia

The difference in spherically equivalent refraction between the two eyes of all measurements was: $\leq$ 1 D in 84%, $\leq$ 2 D in 98%, with a maximum difference of 3.5 D. On average, it was 0.55 D for the patients with CSNB1 and 0.61 D for the patients with CSNB2 (not statistically different, $P = 0.16$). Performing a linear regression of the anisometropia as function of age did not show a statistically significant nonzero slope ($P = 0.65$). Therefore, we used the average spherically equivalent refraction between the two eyes. Although data from both eyes separately could also have been used in a mixed effects model, the high correlation between the two eyes would yield nearly identical results.

Model Creation

Supplementary Figure S2 shows the refraction data as a function of age while fitting a model with restricted cubic splines with 10 knots. It reveals that at the age of approximately 4 years, there is a quite sudden change in the rate of myopization. At the age of approximately 15 years, the myopization ends. The reason for using 10 knots in the model is that from this number of knots onward, these transitions are quite stable at 4 and 15 years. Because the refraction as a function of age seems to consist of 3 approximately linear branches, the final model is based on linear splines with 2 knots at 4 and 15 years of age.

Model Assumptions Verification

When verifying the assumptions of the linear mixed effects model with linear splines, the data look quite homoscedastic. Only at very young ages (0–2 years), the variance seems a bit larger (see Supplementary Fig. S3), possibly due to some deviation from the linearly assumed model or more measurement error. When assessing the normality distribution of the residuals, the Q-Q plot shows that the data are heavy tailed, albeit quite symmetrically (see Supplementary Fig. S4). Therefore, confidence intervals are also determined using bootstrapping ($n = 500$), but this showed that the normality violation actually hardly has an effect on the determination of the confidence intervals. This insensitivity to deviations from normality has also been described before.[27,28]

Fixed Effects

Figure 1 shows all patient data. In addition, the fitted curve based on the linear mixed effects model is plotted in red. It clearly shows that most of the myopization in patients with CSNB occurs in the first years of life and after the age of approximately 4 years myopization is relatively minor. The slope in the 4 to 15 years age range is −0.12 D/year, whereas, after the age of 15 years, the refraction is stable

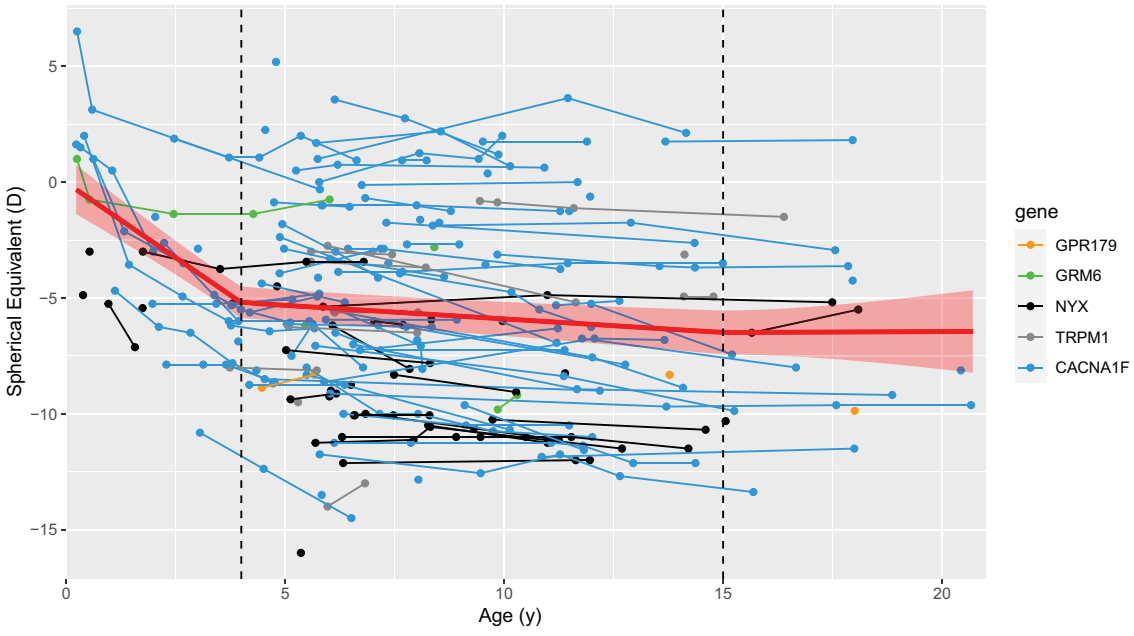

Figure 1. Refraction as a function of age for all CSNB patient data. Red line/area: fit using a model with linear splines and two knots at the age of 4 and 15 years (based on the transition points when fitting restricted cubic splines with many knots, see Supplementary Fig. S2).

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Table 2. Main Parameters of the Three Branches of the Mixed Model With Linear Splines

	Number of Patients	Number of Measurements 0–4 Y/4–15 Y/15–20 Y	Slope (95% CI) 0–4 Y	Slope (95% CI) 4–15 Y	Slope (95% CI) 15–20 Y
All data*	127	46/230/19	−1.29 (−1.53 to −1.06)	**−0.12** (−0.19 to −0.04)	0.01 (−0.25 to 0.27)
All data†	127	46/230/19	−1.28 (−1.49 to −1.07)	**−0.12** (−0.17 to −0.06)	0.02 (−0.21 to 0.24)
All data <0 D†	114	36/202/18	−0.74 (−0.98 to −0.50)	**−0.15** (−0.20 to −0.10)	0.07 (−0.12 to 0.26)
All data <−3 D†	95	27/166/16	−0.89 (−1.20 to −0.57)	**−0.13** (−0.18 to −0.08)	0.08 (−0.11 to 0.25)
All data <−6 D†	64	11/117/12	−0.98 (−1.52 to −0.43)	**−0.13** (−0.18 to −0.08)	0.03 (−0.17 to 0.24)
All data CSNB1†	48	12/76/6	−0.37 (−0.61 to −0.15)	**−0.10** (−0.17 to −0.03)	0.26 (−0.09 to 0.61)
All data CSNB2†	79	34/154/13	−1.61 (−1.86 to −1.36)	**−0.13** (−0.19 to −0.07)	−0.01 (−0.25 to 0.24)

The slopes represent the fitted mean change in refraction in diopters per year.
95% CI, 95% confidence interval.
* The first data row gives the result of the model including also a random slope effect for each patient.
† The data in the remaining rows of the table were determined with the model without the random slope.

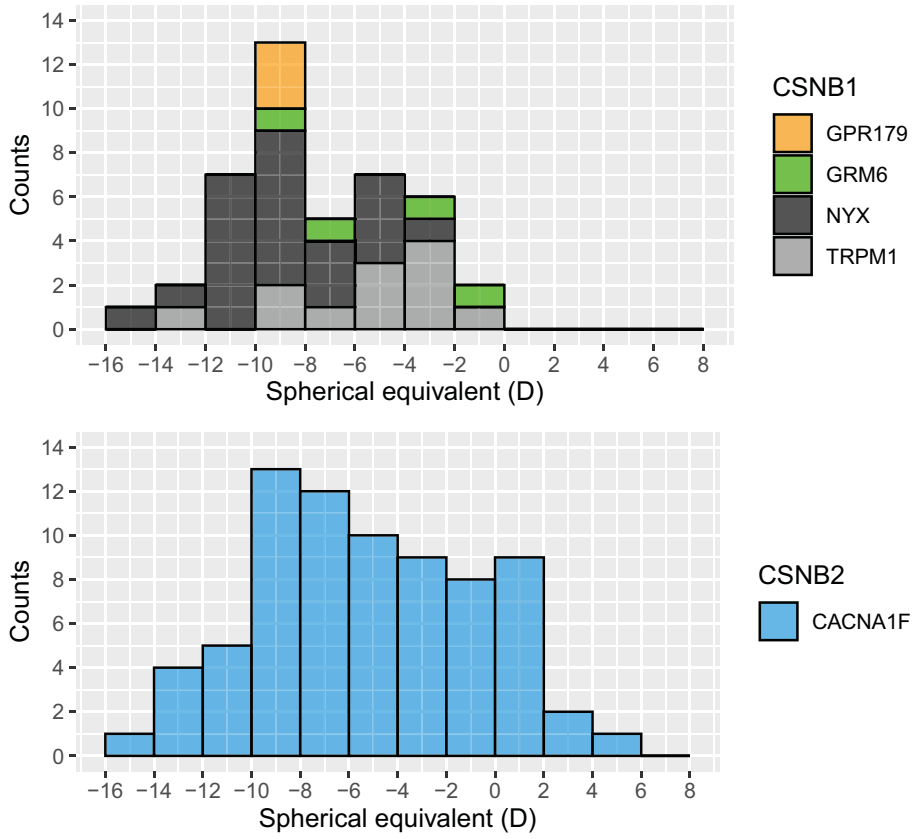

Figure 2. Distribution of the last refraction datapoint of patients with CSNB1 versus patients with CSNB2 (age > 4 years).

at 0.01 D/year. This means that after the age of 4 years, the mean change in refraction would be a total of −1.3 D. The 95% confidence interval of the slope of the 4 to15 years branch (−0.19 to −0.04, see the first row in Table 2) indicates that this myopization is statistically significant different from zero.

Random Effects

The analysis of the random effects of the model (intercept and age-dependency of different patients, see Supplementary Table S2) shows that differences in age dependencies (slopes) only contribute 0.4% to the variance in refrac-

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tive errors between patients. The main contribution in variance between patients is caused by differences in intercept (96.5%). The residuals account for 3.1%. Because the random slope effects of the model only has a minimal effect on the variance in refractive errors between the patients, this random effect was excluded from the model in further analyses of smaller subsets of data (e.g. only patients with CSNB1). The first two rows of data in Table 2 show that indeed the model with and without the random slope hardly changes the fitted mean slopes.

Subsets of Data

Table 2 contains the slopes of the model when including all of the data and subsets of data. When analyzing only data from patients with myopia (<0 D, <−3 D, and <−6 D), the trend in the fitted curve stays the same: a relatively rapid myopization until 4 years of age, from 4 to 15 years only a minor continuation of the myopization, and after the age of 15 years there is no myopization anymore. The slopes at 4 to 15 years for the different myopia subsets show that the values are quite similar, indicating that the (minor) amount of myopization after the age of 4 years does not seem to be correlated with the final level of myopia. This can also be seen from the correlation between the fixed effects slope of the first branch (0–4 years) and second branch (4–15 years) of the fitted model, which is only −0.08 when looking at all the data.

Comparing the 83% confidence intervals of the slopes of patients with CSNB1 (−0.54 to −0.22) and patients with CSNB2 (−1.78 to −1.43), the rate of myopization is statistically different for an age < 4 years. However, the rate of myopization at the age range of 4 to 15 years is not statistically significant different (83% confidence intervals −0.14 to −0.05 and −0.17 to −0.08).

Figure 2 shows histograms of the last refraction measurement of each patient if this measurement was at an age > 4 years. The mean/median refraction for patients with CSNB1 was −7.5 D/−8.1 D and for patients with CSNB2 it was −5.1 D/−5.2 D, which is a statistically significant difference ($P = 0.0043$). None of the patients with CSNB1 (0/43) were hyperopic, whereas 16% (12/74) of the patients with CSNB2 were hyperopic.

Discussion

Our results show that refractive error in patients with CSNB increases quickly toward myopia in the first 4 years of life. After that, progression is only minimal at a rate of −0.12 D/year up to 15 years of age.

For this study, we included only data of patients with a combination of an evident CSNB phenotype (including a pathognomonic ERG) and a genotype associated with CSNB. More strengths are the availability of detailed clinical information as well as extensive data of refraction over time. Our study also has some limitations. We relied on retrospective data collected over many years. In addition, we did not structurally collect data on other risk factors for myopia, such as ethnicity, education level, and family history of myopia. We think, however, that in monogenetic retinal disorders the influence of these factors may be limited. Furthermore, we assembled extensive data on refractive errors, but data on axial length were largely unavailable. Nonetheless, axial length and refractive error are strongly correlated (correlation coefficient 0.89).[29–31] In addition, it was previously reported that ocular axial length elongation was compatible with the myopic progression rate.[5] Last, most refraction data were obtained from prescriptions of current eyeglasses (65%), whereas 31% of the refraction data was obtained by retinoscopy and 4% from other methods. Although using prescription data from eyeglasses might not accurately represent a patient's current refraction, we verified during the visits that the distance visual acuity was in line with both near visual acuity and previous visual acuity assessments. Additionally, in children < 8 years of age, prescriptions for eyeglasses were always based on cycloplegic refractive measurements.

Moderate to high myopia without underlying IRD typically presents between the ages of 6 and 12 years and tends to progress until the late teenage years.[25,32,33] Our results indicate that the natural course of myopia progression in children with CSNB is significantly different, with minimal progression occurring after the age of 4 years. These findings are in line with prior research indicating that children who exhibit high levels of myopia already in early childhood represent a distinct group compared to school-aged children who develop (high) myopia later in life.[4–6] Emphasis should be placed on the search for underlying disorders in these young children. The clinical and genetic heterogeneity in young children with high myopia is substantial. IRDs – besides CSNB – that are associated with high myopia include retinitis pigmentosa, cone-rod dystrophies, and stationary cone disorders, like blue cone monochromacy and Bornholm eye disease. Moreover, monogenic forms of myopia can be further classified into connective tissue disorders (e.g. Stickler syndrome and Marfan syndrome), monogenic isolated high myopia, and monogenic forms of other ocular pathology (e.g. congenital glaucoma).[18] It is likely that the critical sites for refractive error development vary across these different categories, and may even differ for each specific associated gene. Our study emphasizes the importance of examining refractive development in each of these various forms.

Very recently, a comparable study was published by Igelman et al. about the natural history of myopic progression in patients with CSNB.[22] They found that in 78 patients with CSNB, myopia continued to progress between the ages of 0 and 18 years at rates of −0.25, −0.26, and −0.33 D/year for genotypes CACNA1F, NYX, and TRPM1, respectively. However, they assumed a linear trend for the natural course of the refraction. Because we found that refraction changes at a much higher rate in the early years of life, assuming a single linear trend over the entire age range of 0 to 18 years would lead to an overestimation of the rate of myopization at an age > 4 years. Furthermore, Igelman et al. only included patients who had many (6 or more) refraction measurements and therefore excluded the majority of their patients with CSNB. Including only patients with numerous follow-ups may have introduced a bias in their results, as there might have been specific reasons for these patients to return to the clinic so frequently, given that CSNB is a stationary condition. We therefore think that our results better reflect the natural course of refraction in patients with CSNB. Another large study examined refractive errors in patients with different IRDs.[23] They observed high levels of myopia in patients with CSNB with mutations in *CACNA1F* like we did, as well as high myopia in patients with retinitis pigmentosa with mutations in *RPGR*. In addition, some small

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case series showed refraction data in patients with IRD.[19–21] Wilson et al. followed 17 children with Stickler's syndrome in their first decade of life, and reported that the refractive error changed little during the follow-up period.[34] A study by Van der Sande and coworkers suggested that atropine slowed down axial length progression in four patients with CSNB compared to non-Mendelian myopic matches.[35] The age range of these specific children was between 4 and 8 years of age. However, in the light of our study, it is likely that this outcome merely reflects the natural course of the disease.

Our current study confirms the differences in final refraction between patients with CSNB1 (mean = −7.5 D) and patients with CSNB2 (mean = −5.1 D), which is statistically significant. The difference may be caused by a faster myopization rate and/or a higher myopic starting point in patients with CSNB1 compared to patients with CSNB2. Given the limited availability of only 12 datapoints for patients with CSNB1 before the age of 4 years in our dataset, we cannot draw definite conclusions about this matter. After the age of 4 years, the rate of myopization between patients with CSNB1 and patients with CSNB2 was not statistically significant different anymore. An overview of genetic mutations is provided in Supplementary Table S1. In our current study, we did not investigate the relationship between specific variants and refractive error. However, in previous research, we did not find a genotype-phenotype correlation for different variants in CACNA1F.[10]

Patients with CSNB1 were exclusively myopic, whereas 16% of patients with CSNB2 exhibited hyperopia (see Fig. 2). Although the mechanism of the association between myopia and CSNB is not exactly known, there are some proposed theories.[12,36] Previous findings in mice suggest that diminished levels of natural dopamine or distorted visual input resulting from the ON pathway defect might increase the vulnerability to myopia progression.[37,38] In contrast, the role of the OFF pathway in refractive development has been considered to be more limited.[39] However, a recent paper of Jiang and coworkers found an association between a myopia-risk polymorphism and cone-driven OFF pathway response.[40] This suggests that both ON and OFF pathways, and their relative interactions, may contribute to the development of myopia.

The primary indicators currently used for initiating myopic reduction treatments include age, expected growth rate of axial length, and myopic refractive error.[41] In this large retrospective study, we observed minimal myopia progression in CSNB after the age of 4 years. Therefore, relying solely on these indicators for initiating and monitoring myopia treatment may not be the most appropriate approach in children with CSNB. One could argue that myopia reduction treatment in patients with CSNB should be given before the age of 4 years old. However, commencing treatment in this critical period of visual development may have impact on optimal visual function later in life. Moreover, it is uncertain whether myopic reduction treatments will be effective in children with CSNB, as the underlying mechanism of myopia development and progression remains largely unknown and is likely to be different from myopia without underlying IRD. Our study confirms the need for a critical and individualized approach for myopia control interventions in children with infant-onset high myopia.

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