Title: Characterizing the refractive error in pediatric patients with congenital stationary night blindness: a multi-center study

Precis: Individuals with CSNB tend to be highly myopic from a young age and have progression in their myopia overtime – this is true amongst several different causational genes.

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Competing interests: No competing interest.

Abstract

Background/Aims: Congenital Stationary Night Blindness (CSNB) is an inherited retinal disease (IRD) that is often associated with high myopia and can be caused by pathologic variants in multiple genes, most commonly *CACNA1F*, *NYX*, and *TRPM1*. High myopia is associated with retinal degeneration and increased risk for retinal detachment. Slowing the progression of myopia in CSNB patients would likely be beneficial in reducing risk, but before interventions can be considered, it is important to understand the natural history of myopic progression.

Methods: This multicenter, retrospective study explored CSNB caused by variants in *CACNA1F*, *NYX*, or *TRPM1* in patients who had at least 6 measurements of their spherical equivalent of refraction (SER) before the age of 18. A mixed-effect model was used to predict progression of SER overtime and differences between genotypes were evaluated.

Results: 78 individuals were included in this study. All genotypes showed a significant myopic predicted SER at birth (-3.076D, -5.511D, and -5.386D) for *CACNA1F*, *NYX*, and *TRPM1* respectively. Additionally, significant progression of myopia per year (-0.254D, -0.257D, and -0.326D) was observed for all three genotypes *CACNA1F*, *NYX*, and *TRPM1* respectively.

Conclusions: Patients with CSNB tend to be myopic from an early age and progress to become more myopic with age. Patients may benefit from long term myopia slowing treatment in the future and further studies are indicated. Additionally, CSNB should be considered in the differential diagnosis for early onset myopia.

Key Messages:

What is already known on this topic: CSNB is known to be associated with high myopia in children, however, the nature/progression and genetic basis of this is unknown.

What this study adds: This study suggests that myopia in CSNB patients progresses and this progression is similar amongst disease caused by *CACNA1F, NYX,* and *TRPM1*.

How this study might affect research, practice or policy: CSNB patients may benefit in the future from myopia slowing treatment and practitioners should consider CNSB as a possible diagnosis in early onset high myopia.

INTRODUCTION

Inherited retinal diseases (IRDs) represent a heterogeneous group of ophthalmic conditions resulting from pathologic genetic variants that lead to dysfunction and/or degeneration of specific cell populations in the eye (e.g. photoreceptors, retinal pigment epithelial cells). Several hundred genes are now known to cause different forms of inherited retinal disease.(1) Many of these conditions are also associated with high levels of refractive error, both myopia and hyperopia and abnormalities in axial length.(2, 3) High myopic refractive errors are associated with a variety of ocular comorbidities including retinal detachment, open angle glaucoma, cataracts, and myopic degeneration,(4-8) and the rates of high myopia are rapidly increasing in many parts of the world.(9) For this reason, there is great interest in identifying therapeutic and behavioral interventions to slow the rate of myopia progression in the general population, including the utilization of low dose atropine therapy, specially designed rigid and soft contact lenses and peripherally defocusing spectacle lenses.(10) Given that patients with IRDs often have limited visual potential secondary to retinal degeneration, there is an even greater need to prevent further vision loss as a consequence of pathologic myopia. A critical first step towards this goal is to understand the prevalence, severity, and progression of high myopia among patients with IRDs.

Congenital Stationary Night Blindness (CSNB) is a family of IRDs most of which are characterized by synaptic transmission defects involving the connection between photoreceptors and bipolar cells.(11) Patients generally experience a non-progressive retinal disease frequently characterized by nystagmus, decreased visual acuity, and impaired night vision.(12) CSNB is related to a defect of function and there is no photoreceptor loss with time in most cases. Visual acuity is largely stable over time in this disorder. The major form of CSNB, representing an electronegative electroretinogram can be divided into subgroups: incomplete (i)CSNB, which demonstrates a reduced but present rod response under scotopic conditions and severely reduced photopic responses, representing an ON- and OFF-bipolar cell defect, and complete (c)CSNB, which is characterized by no recordable rod b-wave under scotopic conditions and altered photopic responses, representing an isolated ON-bipolar cell defect.(12-14) While variants in *CACNA1F*(15, 16) and *CABP4*(17) lead to (i)CSNB, variants in *NYX*(18, 19), *GRM6*(20, 21), *TRPM1*(22-24), *GPR179*(25, 26) and *LRIT3*(27) lead to (c)CSNB.(28) The most common forms of CSNB are due to gene defects in *CACNA1F* and *NYX*, which are inherited in an X-linked inheritance pattern, and *TRPM1*, which is inherited in an autosomal recessive pattern.(28, 29) CSNB is typically associated with high myopia and although several prior case series have described the refractive error of individuals with CSNB, there is a paucity of data on the natural history, axial length, severity, variability, and progression of myopia in patients with this condition.(2, 12, 30)

Several landmark clinical trials, including the Atropine for the Treatment Of Myopia 1 (ATOM I), Atropine for the Treatment Of Myopia 2 (ATOM II), and the Low-concentration Atropine for Myopia Progression (LAMP) studies have shown that atropine can effectively reduce the progression of myopia in children without IRDs and that even very low doses (0.01% - 0.05% atropine) are effective.(31-33) However, to date, no study has evaluated the use of myopia slowing treatments such as low dose atropine in patients with CSNB or other IRDs.

Given the increasing rates of high myopia and its associated ocular comorbidities, it is possible that treatment to prevent myopia progression in IRD patients could lead to prevention of further vision loss from the aforementioned comorbidities and increase the number of patients eligible for gene therapy given that high myopia can be an exclusion criterion. The static nature of the retinal disease in CSNB, coupled with the reported high myopia in this population, provides an ideal model to test myopia slowing therapies in the future. Prior to conducting this type of clinical trial, a stronger understanding of the natural history of the refractive error progression in patients with CSNB is needed such that a therapeutic effect can be distinguished from natural history.

Here we describe a multinational, multicenter, retrospective, longitudinal study evaluating the progression of refractive error in patients with CSNB. We also report sub-group comparisons of patients with different CSNB genotypes.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Oregon Health & Science University IRB #2735 and met the tenets of the Declaration of Helsinki.

Data collection

In this multinational, multicenter, retrospective, longitudinal chart review, clinical databases at the participating sites were queried for patients with diagnosed CSNB. Inclusion criteria included age 18 years or younger, pathogenic variants in *CACNA1F, NYX,* and *TRPM1*, and at least six longitudinal refractive error data points from first visit to age 18. *CACNA1F, NYX,* and *TRPM1* were included as they were the most represented genes during preliminary screening of databases and there were not enough data for rigorous evaluation with other genotypes. Subjects with implausible trends in refractive error over time, refractive surgery, or cataract surgery were excluded from the study.

Demographic information (including age at the time of refractive error measurement), clinical information (refractive error), and genotypic data were collected for each subject by authors at their respective clinical sites and sent to the Oregon Health & Science University for analysis. Refractive error was defined as spherical equivalent of refraction (SER).

Data analysis

Mixed-effect models were used to account for potential intra-personal correlations. Random intercept and random slope were included in the models with SER as the outcome; gene, age, and the interaction between gene and age as the independent variables; and subject as the grouping variable. To better understand the natural history of myopic progression, SER at birth and expected change in SER per year of age were predicted. SER at birth was used our model and extrapolated the predicted SER at age 0. Although subjects may not have been myopic or had this SER at birth and may have merely progressed quickly in the first few years of life, this still gives a variable that suggests the severity of early SER in these patients and was therefore used as an outcome variable. These were calculated using the mixed-effect model and compared across three genes: *CACNA1F*, *TRPM1*, and *NYX*. From the mixed-effects model, conditional intraclass correlation coefficients (ICC) were calculated for each gene and compared. A higher ICC (closer to 1) implies the total variance over time is largely explained by individual variation rather than variability in measurement

suggesting a high level of SER reliability. Trend analysis of the subjects with *TRPM1* genes and myopic subgroup were performed similarly by mixed-effects models. A p-value less than 0.05 was considered statistically significant and Bonferroni correction was used to adjust p-values for a multiple test correction.

RESULTS

All Subjects

Subject Characteristics

A total of 390 potential subjects were identified. Subjects that were older than 18 (79 subjects), had less than six visits (301 subjects), or had genetics variants in CSNB genes other than *CACNA1F, NYX,* and *TRPM1* (5 subjects) were excluded. From there, one excluded subject had very large residuals from mixed-effects linear regression due to random changes in SER of 10 or more over the course of a few years. Three additional subjects were removed due to large, non-linear changes in SER deemed to be likely chart recording errors. Finally, two subjects were removed as their SER showed a positive trend. Both of these subjects were hyperopic at enrollment and had *CACNA1F* variants. Among the subjects excluded, four of the subjects had pathogenic variants in the *CACNA1F* gene and two subjects had pathogenic variants in the *NYX* gene.

Seventy-eight subjects were included in this study (Table 1). Forty-one subjects had pathogenic variants in *CACNA1F*, 22 subjects had pathogenic variants in *NYX*, and 15 subjects had pathogenic variants in *TRPM1*. Of the 78 subjects, 69 were myopic at the first visit. The mean (SD) age for the youngest visit were 3.82 (2.73), 3.15 (2.41) and 2.91 (3.16) years for *CACNA1F, NYX*, and *TRPM1* respectively. The mean (SD) age for the oldest visit were 13.2 (3.44), 13.8 (2.89), and 12.4 (3.89) years for *CACNA1F, NYX*, and *TRPM1,* respectively. One CACNA1F subject was female and she was homozygous – further details about her and her family were recently described.(34) There were roughly equal males and females within the *TRPM1* gene group. There were no females with *NYX* variants (X-linked) and only one female with a *CACNA1F* variant (X-linked). Average length of follow up was 9.36 years, 10.6 years, and 9.49 years in the *CACNA1F*, *NYX*, and *TRPM1* groups respectively. Demographic data is detailed in Table 1. Further information on the specific genetic variants of these 78 individuals are included in supplemental Table 1.

All Subject Analysis

CACNA1F, *NYX*, and *TRPM1* subjects all had predicted SERs at birth extrapolated from the aforementioned mixed-effect model that were significantly myopic ($p < 0.001$). Those with *NYX* pathogenic variants had the most highly myopic SER at birth, followed by those with *TRPM1* pathogenic variants, then those with *CACNA1F* pathogenic variants. The expected SER at birth was significantly less myopic in those with *CACNA1F* pathogenic variants as compared to those with *NYX* pathogenic variants ($p = 0.014$). There were no significant differences in the expected SER at birth from pair-wise comparisons of *NYX* vs *TRPM1* or for *TRPM1* vs *CACNA1F*. All three gene groups had an expected myopic shift per year ($p < 0.001$). There was no significant difference in the expected change in SER per year of age from pair-wise comparisons of the genes (Table 2).

For subjects with autosomal recessively inherited *TRPM1* disease, comparing SER and myopic trend over time in females vs males showed that females and males with *TRPM1* pathogenic variants had an expected SER at birth that was significantly less than zero ($p < 0.001$) i.e myopic and females had a significantly more myopic SER at birth than males ($p = 0.012$). Both females and males with *TRPM1* pathogenic variants were found to become significantly more myopic overtime ($p < 0.001$). Furthermore, males were found to have a significantly higher myopic shift per year than females ($p = 0.014$; Table 3).

Initially Myopic Subjects

Myopic Subject Analysis

A major future goal is to study therapies that prevent myopic progression such as low dose atropine in patients with CSNB. Given that these future trials would exclude subjects who present with a hyperopic SER, a second sub-analysis was conducted for this study to better characterize the patients with myopic SER at presentation (SER < 0D).

For these subjects, all three genotypes had an expected SER at birth that was significantly myopic ($p < 0.001$). There was no significant difference in the expected SER at birth from pair-wise comparisons between the three genes. All three genes showed that subjects became significantly more myopic overtime ($p < 0.001$). There was no significant difference in the expected change in SER per year of age from pair-wise comparisons between the genes (Table 4).

DISCUSSION

This study aimed to better characterize the severity and progression of refractive errors in children with CSNB caused by pathogenic variants in the most commonly involved genes *CACNA1F*, *NYX*, and *TRPM1*. Considering all CSNB subjects together, this model demonstrated that all three genetic background showed, on average, a myopic refractive error, corroborating previous reports that CSNB patients tend to be myopic.(2, 12, 30) Subjects in the *CACNA1F* group were the least myopic overall, while subjects in the *NYX* group were the most myopic at birth. This finding corroborates a study by Hendricks *et al.* who showed the *NYX* related disease has some of the most highly myopic refractive errors among many different IRDs (not just within CSNB).(2) This same study also suggested a highly myopic phenotype in *TRPM1* associated disease, which is also supported by the current data.(2) The differences in refractive errorS may be due to the differences between (i)CSNB and (c)CSNB.(35) Our study used predicted SER at birth as a proxy although this may be a better proxy for progression within the first two years. It is unclear if patients start emmetropic and then progress quickly during their first two years of life before most measurements are taken. However, predicted SER at birth remained a useful metric to compare across genotypes.

The current study also suggested that there was a significant difference in SER only between *CACNA1F* and *NYX* and that the difference in SER between *CACNA1F* and *TRPM1* and between *NYX* and *TRPM1* were not statistically significant. Additionally, subjects with *CACNA1F* pathogenic variants had the broadest range of refractive errors: 8/41 (19.5%) of the *CACNA1F* subjects started with a hyperopic refraction compared to only 1/22 (4.5%) for *NYX* and 0/15 (0.0%) for *TRPM1*. For reasons poorly understood, this might be related to complete ON-pathway dysfunction due to variants in the latter two genes as described

previously in patients with (c)CSNB versus patients with (i)CSNB still having partial ON-pathway function.(35) There was no difference in the overall expected change in SER per year between genotypes, and our model showed a statistically significant myopic progression for all three gene defects ranging from -0.254D to -0.326D per year. This suggests that, although the average pediatric *CACNA1F* patient may start less myopic than the average *NYX* patient, all three genotypes tend to progress at the same rate each year and will gain 1 diopter of myopic progression every 3 to 4 years. In the atropine treatment of myopia trial in non-IRD children with myopia, children progressed by -1.20D over two years.(31) That said, it is easy to miss the diagnosis of CSNB without an electroretinogram. Therefore, a future trial investigating myopia progression prevention therapy in CSNB may need to be longer than the ATOM studies to evaluate the same endpoint. However, given that CSNB patients often start moderately to highly myopic, prevention even of a slower progression might still be expected to be beneficial in preventing further vision impairment associated with myopia.

Interestingly, female patients with *TRPM1* variants started more myopic than males, however, males progressed at a faster rate. The cause of this is unknown although this suggests that males may, overtime, become more myopic than females with *TRPM1* variants without intervention. However, this model only looked at ages 0-18 and further extrapolation may be limited.

The primary future goal is to perform a prospective treatment trial utilizing myopia progression therapies in patients with CSNB. Understanding the rate of progression and the differences between genotypes is therefore paramount before starting such a trial. There was no significant difference in the year over year expected progression in SER between all three genotypes. As long as the natural history of progression per gene is known, future trials will not likely need to be gene-specific, and myopic patients with *CACNA1F*, *NYX*, and *TRPM1* pathogenic variants may all benefit from treatment with low dose atropine. CSNB is uniquely situated to benefit from slowed progression of myopia with possible interventions given the stability of the retina otherwise. Given that CSNB is a non-progressive disease, much of the progression in decreased vision may be associated with worsening myopia and the effects on the retina thereof suggesting that treatment for myopia in patients with CSNB may provide a large benefit to maintaining their vision.

An additional future direction includes further elucidation of the similarities and variability in refractive error specifically within the *CACNA1F* patients. Further elucidation into the similarities and differences in the hyperopic patients is indicated. It is possible that the variability is driven by differences in incomplete vs complete CSNB. Previous studies have suggested that the ON bipolar cell pathway implicated in complete CSNB may, at least in part, be driving the myopia and could explain some differences in the variability between patients.(35) This could help explain why there was increased variability in *CACNA1F* vs *NYX*, and *TRPM1* and why there were hyperopic patients with *CACNA1F* variants but not *NYX* and *TRPM1.* Further analysis into the genotypes and variability was outside the scope of this study but is currently a focus for this group on future analyses.

There were several limitations to our study. There were limited data on infants, with most first measurements occurring after the age of 2 years in this data set. This study did not

include data on parental refractive error which is a strong predictor for refractive error in children. These data are also retrospective and there were several methods of measuring SER (e.g. cycloplegic autorefraction, cycloplegic retinoscopy, manifest refraction) and these methods varied between subjects and between visits of the same subject. Additionally, axial length was not measured, and SER was used as a surrogate. Finally, while this cohort was large, it was primarily from Western sites; given the high prevalence of myopia in East Asia and possible variability in different groups, further study with a more diverse population would be beneficial. Future directions include evaluating the progression of myopia in adult CSNB patients and evaluation of other causative genes.

Overall, these data suggest a moderate to high myopia phenotype that progresses throughout childhood and early adolescence, making CSNB an ideal candidate for an early treatment trial into the efficacy of the use of low dose atropine in slowing myopia progression in IRDs and thereby reducing further vision loss. In addition, CSNB should always be considered as a potential cause of early onset myopia. We developed a model that increases our understanding of the natural history of refractive error progression in individuals with CSNB. Given the rarity of CSNB and the likelihood of underdiagnosed cases, a placebo-controlled trial may not have the statistical power to evaluate effectiveness. Therefore, this study will be even more useful in the future and gives us an estimated rate of progression and degree of myopia in patients with CSNB to compare this treated group to in the future. Additionally, amongst patients that began myopic (i.e. the population that a future treatment trial would enroll), there was no significant difference in the degree of initial myopia or rate of progression between the three genes evaluated suggesting that all three genes could be included in this future trial.

Tables and Figures

Table 1: Demographics of subjects

		CACNA1F (n=41)	*NYX* (n=22)	*TRPM1* (n=15)	Overall (n=78)
Sex	Male (%)	40 (97.6)	22 (100)	7 (46.7)	69 (88.5)
	Female (%)	1 (2.4)	0 (0)	8 (52.3)	9 (11.5)
Age first visit (years)	Mean (SD)	3.82 (2.73)	3.15 (2.41)	2.91 (3.16)	3.46 (2.72)
	Median [Min, Max]	3.00 [0.07, 13.00]	2.50 [0.40, 7.00]	1.10 [0.33, 10.00]	3.00 [0.07, 13.00]
SER first visit (diopters)	Mean (SD)	-4.54 (4.74)	-5.77 (3.48)	-5.95 (3.40)	-5.16 (4.18)
	Median [Min, Max]	-4.00 [-13.5, 5.13]	-6.13 [-13.10, 1.50]	-6.13 [-13.50, -1.50]	-5.56 [-13.5, 5.13]
Age last visit (years)	Mean (SD)	13.2 (3.44)	13.8 (2.89)	12.4 (3.89)	13.2 (3.37)
	Median [Min, Max]	14.0 [6.00, 18.00]	14.0 [9.00, 18.0]	11.0 [6.00, 18.0]	14.0 [6.00, 18.0]
SER last visit (diopters)	Mean (SD)	-6.86 (5.57)	-8.73 (4.25)	-9.29 (4.25)	-7.85 (5.09)
	Median [Min, Max]	-7.63 [-23.0, 4.13]	-9.63 [-15.5, -1.00]	-8.50 [16.5, -1.00]	-7.94 [-23.0, 4.13]
First vs last age (years)	Mean (SD)	9.36 (2.89)	10.60 (2.86)	9.49 (2.83)	9.74 (2.89)
	Median [Min, Max]	9.00 [5.00, 16.00]	10.2 [6.75, 16.0]	10.0 [5.00, 14.50]	9.58 [5.00, 16.00]

Table 2: Summary of analysis of all subjects (N=78)

Gene/Comparison	Expected SER at Birth[a,b] (95% CI)	Expected changes in SER at per year[a,b] (95% CI)	Conditional Intraclass Correlation Coefficient (ICC)
CACNA1F	-3.706 (-4.558, -2.855)***	-0.254 (-0.311, -0.196)***	0.926
NYX	-5.511 (-6.63, -4.359)***	-0.257 (-0.333, -0.181)***	0.8515
TRPM1	-5.386 (-6.783, -3.989)***	-0.326 (-0.421, -0.232)***	1.00
NYX vs *TRPM1*	-0.125 (-1.935, 1.686)	0.07 (-0.051, 0.191)	N/A
CACNA1F vs *NYX*	1.805 (0.372, 3.237)*	0.003 (-0.092, 0.098)	N/A
TRPM1 vs *CACNA1F*	-1.68 (-3.316, -0.044)	-0.073 (-0.183, 0.038)	N/A

[a] Expected values are from a mixed-effects random intercept/random slope model with subject as the random component

[b] $p<0.05/3$*, $p<0.01/3$**, $p<0.001/3$***

Table 3: Summary of Analysis of TRPM1 Subjects (n=15)

Sex	Expected SER at Birth[a,b] (95% CI)	Expected Change in SER per Year[a,b] (95% CI)
Male	-3.872 (-5.442, -2.302)***	-0.44 (-0.557, 0.323)***
Female	-6.596 (-8.027, -5.164)***	-0.247 (-0.346, -0.148)***
Female – Male	-2.723 (-4.848, -0.599)*	0.193 (0.04, 0.346)*

Table 4: Summary of Analysis of Myopic Subjects (n=69)

Gene/Comparison	Expected SER at Birth[a,b] (95% CI)	Expected changes in SER at per year[a,b] (95% CI)	Conditional Intraclass Correlation Coefficient (ICC)
CACNA1F	-5.07 (-5.909, -4.231)***	-0.265 (-0.329, -0.201)***	0.891
NYX	-5.791 (-6.832, -4.749)***	-0.262 (-0.340, -0.184)***	0.8308
TRPM1	-5.395 (-6.628, -4.162)***	-0.325 (-0.420, -0.231)***	0.8456
NYX vs *TRPM1*	-0.396 (-2.010, 1.219)	0.064 (-0.059, 0.186)	N/A
CACNA1F vs *NYX*	0.721 (-0.616, 2.058)	-0.003 (-0.104, 0.098)	N/A
TRPM1 vs *CACNA1F*	-0.325 (-1.817, 1.116)	0.061 (-0.175, 0.053)	N/A

[a] Expected values are from a mixed-effects random intercept/random slope model with subject as the random component

[b] $p<0.05/3$*, $p<0.01/3$**, $p<0.001/3$***

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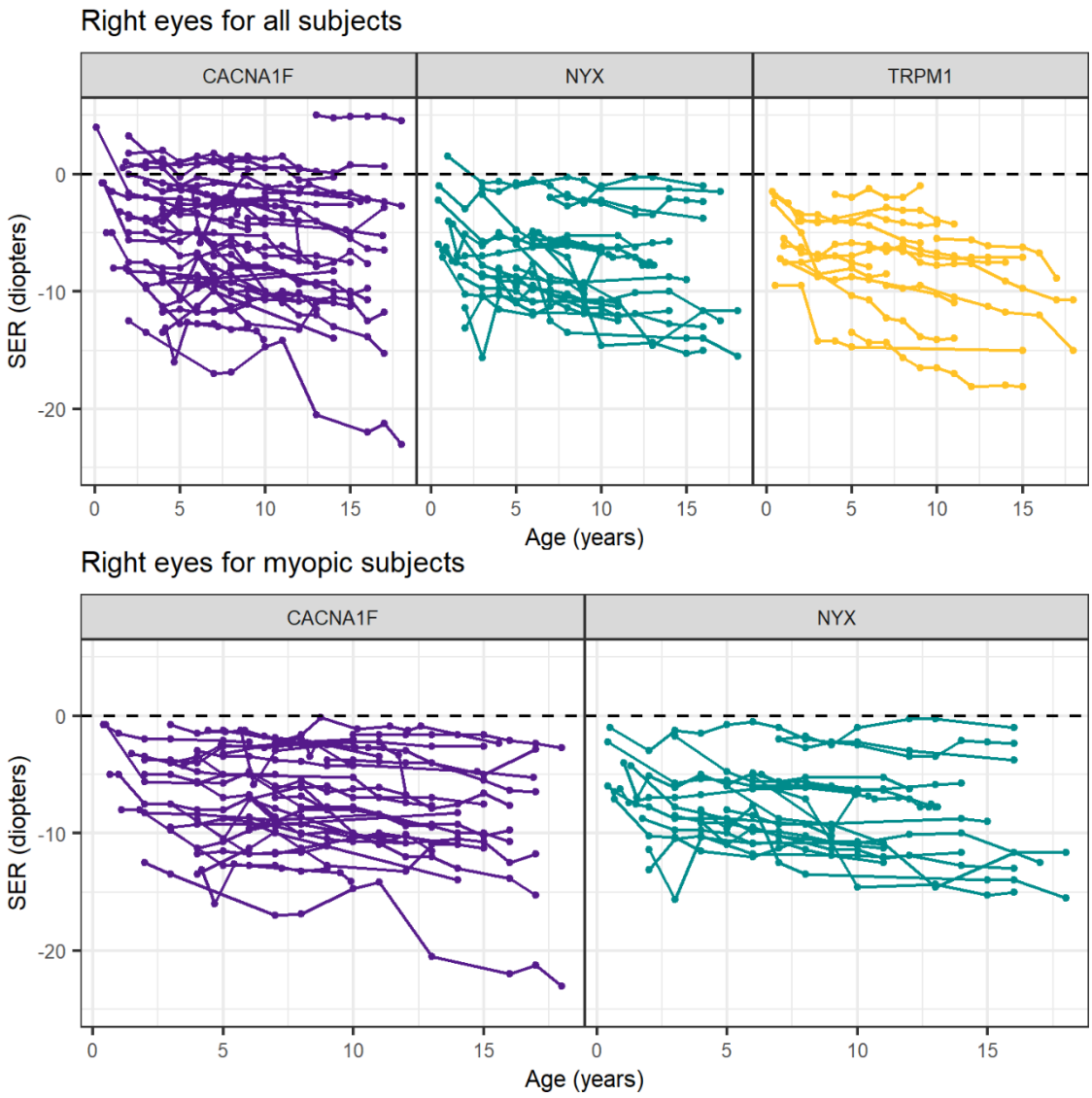
Figure legends:

Figure 1: Spaghetti plot showing the trend of SER in patients with variants in *CACNA1F, NYX,* and *TRPM1*. Each line represents the right eye of one patient overtime. Bottom panels represent patients that began myopic and had variants in *CACNA1F* and *NYX.*



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