• Investigation •

Genotype-phenotype correlations in Chinese patients with congenital stationary night blindness and early-onset high myopia: evidence from electrophysiology and whole-exome sequencing

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Abstract

● **AIM:** To identify pathogenic variants in families with congenital stationary night blindness (CSNB) accompanied by early-onset high myopia (eoHM) using whole-exome sequencing (WES), and to evaluate the clinical value of electrophysiological and genetic testing for the differential diagnosis of CSNB, which is frequently misdiagnosed as amblyopia.

● **METHODS:** The study cohort comprised families clinically diagnosed with eoHM. Probands and available family members underwent comprehensive ophthalmic examinations. Pathogenic variants were identified *via* WES, *in silico* analysis, co-segregation analysis, Sanger sequencing and classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Genotype-phenotype correlations were analyzed within the context of CSNB, supplemented by a review of relevant literature utilizing databases including HGMD, PubMed, CNKI, and Wanfang.

● **RESULTS:** Among 42 families with eoHM, five were identified with CSNB. The probands aged 2–5y, with spherical equivalents (SE) ranging from −6.00 to −11.00 D and best-corrected visual acuity (BCVA) between 0.15 and 0.6. No organic ocular abnormalities were observed. Initially diagnosed as high myopia and refractive amblyopia, they received optical correction and amblyopia therapy. Electroretinogram (ERG) revealed diminished rod responses and a negative waveform under dark-adapted 3.0 ERG conditions. Seven pathogenic variants were identified in *CACNA1F*, *NYX*, and *TRPM1*, including two novel variants. All five probands were ultimately diagnosed with CSNB-associated eoHM. In Family 1, the proband carrying a *CACNA1F* variant (c.1873C>T; p.Arg625Ter) exhibited slow myopic progression without fundus changes over 9y of follow-up. A literature review highlighted significant genetic and clinical heterogeneity in CSNB-related eoHM.

● **CONCLUSION:** This study reveals marked genetic and clinical heterogeneity in CSNB-related eoHM. *TRPM1* and *NYX* variants (complete CSNB) cause earlier and more severe myopia than *CACNA1F* variants (incomplete CSNB). Characteristic ERG patterns differentiate subtypes. Reduced BCVA in eoHM may indicate inherited retinal disorders, not just refractive errors. Children with eoHM and reduced BCVA need systematic electrophysiological and genetic evaluations to prevent misdiagnosis and enable personalized care.

● **KEYWORDS:** early-onset high myopia; congenital stationary night blindness; amblyopia; electroretinography; gene; mutation

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INTRODUCTION

Congenital static night blindness (CSNB) is a highly heterogeneous hereditary retinal disorder (IRD)[1]. It is predominantly characterized by static night blindness and impaired dark adaptation, frequently accompanied by early-onset high myopia, strabismus, nystagmus, and a decline in visual acuity. In 1952, Schubert and Bornschein[2] reported the most prevalent electroretinogram (ERG) abnormality in CSNB. In this abnormality, the full-field electroretinogram (ffERG) dark response demonstrates a normal a-wave amplitude but a significantly reduced b-wave amplitude, resulting in a typical negative ERG. This indicates that the dysfunction in this type of CSNB occurs subsequent to phototransduction, primarily affecting the signal transmission between photoreceptors and bipolar cells. In 1986, Miyake *et al*[3] further classified Schubert-Bornschein type CSNB into complete CSNB (cCSNB) and incomplete CSNB (iCSNB) based on distinct ERG manifestations. The former is characterized by a complete loss of the rod cell b-wave and oscillatory potentials in the dark response, while the cone a-wave amplitude remains approximately normal, along with a complete loss of dark adaptation. The latter shows a reduction in the rod cell b-wave, cone a-wave, and 30 Hz flicker response in the dark response, while the oscillatory potentials remain entirely normal, accompanied by a significantly decreased dark adaptation. The inheritance patterns include autosomal dominant (AD), autosomal recessive (AR), or X-linked[4]. Among these, X-linked inheritance is the most common (57.9%), followed by AR and sporadic cases (40%), whereas AD is the rarest (2.1%)[5]. To date, more than 20 CSNB-related pathogenic genes have been identified, with over 500 distinct mutations and more than 670 affected alleles associated with CSNB[6-8]. Although CSNB has a low incidence and is regarded as a rare disease, its actual prevalence may be underestimated due to its insidious onset. Early-onset high myopia (eoHM) is the most common clinical manifestation (accounting for 96.61% of cases), followed by nystagmus (62.71%) and strabismus (52.54%)[9]. The phenotype of iCSNB is more heterogeneous than that of cCSNB, especially in cases with mutations in the *CACNA1F* gene, where patients rarely or never present with night blindness. ERG plays a crucial role in the diagnosis, classification, and treatment guidance of CSNB. Amblyopia refers to a decline in the best-corrected visual acuity (BCVA) of one or both eyes during visual development due to abnormal visual experiences, with no organic lesions detected during ophthalmic examination. Due to the mild symptoms of CSNB patients, who often present with early-onset myopia or hyperopia, normal fundus findings, and the frequent neglect of retinal function testing in clinical practice, CSNB is easily misdiagnosed as amblyopia. This study aimed to analyze the association between genotype and phenotype in patients with eoHM who exhibit a decline in BCVA, using a combined electrophysiological-genetic approach. Additionally, a literature review was conducted to analyze previously reported genetic eye diseases associated with CSNB and accompanied by eoHM, with the aim of achieving precise differential diagnosis. Given that the Schubert-Bornschein type of CSNB is the most prevalent, this study exclusively centers on this subtype to carry out a comprehensive analysis of its pathogenic genes and pathological mechanisms, and to summarize the genotype-phenotype correlation.

PARTICIPANTS AND METHODS

Ethical Approval This research was carried out at the Gansu Aier Ophthalmology and Optometry Hospital. The study was reviewed and approved by the Ethics Committee for Human Research (Approval No. GSAIER2023IRB04) and was conducted in line with the guidelines of the Declaration of Helsinki. Written informed consent was acquired from all the participants included in the study or their legal guardians prior to their participation.

Participants The proband's family reported high myopia before school age. High myopia was diagnosed at our or other hospitals, defined as spherical equivalent (SE) refractive error ≤-6.00 diopters (D) or axial length >26 mm. Inclusion criteria were: 1) high myopia at preschool age (<7y); 2) no conditions causing secondary high myopia; 3) no systemic abnormalities during follow-up.

Clinical Evaluations Comprehensive ophthalmic examinations were conducted on all probands and their family members, encompassing slit-lamp microscopy, indirect ophthalmoscopy, BCVA, color vision testing (Ishihara Color Vision Test, 5th Edition, by Yu Ziping), wide-field color fundus photography (Optos Daytona P200T), spectral-domain optical coherence tomography (OCT; HD-OCT 4000, Carl Zeiss Meditec, USA) and ffERG (LCK Technologies, USA). Detailed medical histories were collected and documented, including the current medical history, past medical history, personal history, family history, and reproductive history, and pedigrees were constructed.

Whole-Exome Sequencing Whole-exome capture was conducted utilizing the Agilent SureSelect Exon Capture Kit, succeeded by high-throughput sequencing on an Illumina platform with an average coverage depth of 100×. The raw sequencing data were processed *via* Illumina Basecalling Software v1.7 and aligned to the human reference genome (NCBI build 37.1) from the National Center for Biotechnology Information (NCBI). Single nucleotide variants (SNVs) and insertions/deletions (Indels) were identified respectively by means of SOAP software (http://soap.genomics.org.cn) and BWA software (http://bio-bwa.sourceforge.net) to acquire all

DNA sequence variations existing in the samples. Variants with a minor allele frequency (MAF) >1% in public databases (db135) were filtered out, along with variants predicted to exert no influence on protein structure or function. Subsequent to stepwise filtering, variants shared by all affected family members were identified, and those also present in unaffected relatives were excluded to obtain candidate pathogenic variants. Candidate variants were validated through Sanger sequencing to eliminate false positives and further confirmed by segregation analysis between genotypes and phenotypes within the family.

Pathogenicity Analysis of Variants

***In silico* analysis** Allele frequencies of East Asian populations were sourced from the 1000 Genomes Project (http://browser.1000genomes.org) and the Exome Aggregation Consortium database (ExAC, http://exac.broadinstitute.org), with an MAF<0.005 serving as the threshold to exclude benign variants. Pathogenicity predictions were carried out using multiple bioinformatics tools, including PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2), SIFT (http://sift.jcvi.org), PROVEAN (http://provean.jcvi.org/index.php), and MutationTaster (http://www.mutationtaster.org). Conservation analysis of variant sites was performed utilizing the online tool Multalin (http://sacs.ucsf.edu/cgi-bin/multalin.py). The three-dimensional structure of the normal protein was predicted using AlphaFold, and visualization of mutant protein structures was conducted with PyMOL software. Classification of Variations: The pathogenicity of variants was classified into five categories “pathogenic”, “likely pathogenic”, “uncertain significance”, “likely benign”, and “benign” according to Standards and Guidelines for Sequence Variants Interpretation issued by American College of Medical Genetics and Genomics (ACMG) in 2015.

Literature review Employing the search terms “CSNB” and “eoHM”, we conducted searches in the HGMD database, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Medical Database to identify reported cases of eoHM associated with CSNB. We extracted cases of eoHM related to CSNB and analyzed and summarized their genotypes and clinical phenotypes. Inclusion criteria for the literature were as follows. Study type: only clinical studies were included, while conference abstracts were excluded. Study methods: they should be comparable to the present study. Clinical data: complete clinical information that supports genetic findings and provides specific diagnostic criteria for the disease.

RESULTS

Clinical Phenotypes Among the 42 families with eoHM recruited in this study, five probands were ultimately diagnosed with CSNB. The age at initial presentation ranged from 2 to 5y. The SE refractive error ranged from -6.00 to -11.00 D, and the BCVA ranged from 0.15 to 0.6 (decimal). All cases were initially diagnosed with high myopia accompanied by refractive amblyopia and underwent long-term spectacle correction and amblyopia training. The interval from initial presentation to definitive diagnosis ranged from 0.5 to 9y. Fundus examinations revealed no organic lesions. ffERG demonstrated significantly reduced rod responses, with cone function being normal or mildly to moderately reduced, and a negative configuration of the dark-adapted 3.0-ERG (b/a) waveform. Family 1 (F1) and Family 2 (F2) presented with iCSNB, whereas Family 3 (F3), Family 4 (F4), and Family 5 (F5) presented with cCSNB. The details of the phenotypes are presented in Table 1.

Genetic Findings Seven pathogenic variants in *CACNA1F*, *TRPM1*, and *NYX* genes were detected in 5 probands, including: F1: a hemizygous nonsense variant c.1873C>T (p.Arg625Ter) in *CACNA1F*; F2: a hemizygous nonsense variant c.244C>T (p.Arg82*) in *CACNA1F*; F3: a hemizygous in-frame deletion c.70_93del (p.Arg24_Ala31del) in *NYX*; F4: compound heterozygous variants c.2130T>A (p.Tyr710*) and c.1089+1G>A (splice-site) in *TRPM1*; F5: compound heterozygous variants c.2984T>C (p.Met995Thr) and c.1089+1G>A (splice-site) in *TRPM1*. Among the seven identified variants, two are novel. Consequently, all five probands were diagnosed with CSNB combined with eoHM. Mode of inheritance analysis indicated that three families exhibited X-linked recessive inheritance and two showed autosomal recessive inheritance, and the genetic testing results are summarized in Table 2.

Genotype and Phenotype Analysis In F1, the proband was a 12-year-old male who visited Ningxia Eye Hospital due to substandard corrected visual acuity in both eyes. The proband did not manifest symptoms of night blindness. At the age of 3y, the patient was misdiagnosed with bilateral high myopia accompanied by amblyopia and then received long-term treatment, including wearing glasses and undergoing amblyopia training. The patient was followed up for 9y (Table 3). During this period, the SE of the right eye (OD) increased by -1.75 D (-0.19 D per year), and that of the left eye (OS) increased by -2.75 D (-0.31 D per year). The clinical manifestations and genetic test results of the patient are presented in Figure 1. The proband was finally diagnosed with iCSNB combined with eoHM. Whole-exome sequencing identified a hemizygous nonsense variant, c.1873C>T (p.Arg625Ter), within the *CACNA1F* gene, which resulted in premature termination and protein truncation at codon 625. Sanger sequencing indicated that the mother moderately carried the identical heterozygous variant. A nonsense variant in myopia has been previously documented in numerous

Table 1 Clinical data of probands from five CSNB families

Proband	Age	Sex	UCVA		BCVA		IOP (mm Hg)		Axial length (mm)		Nyctalopia	Strabismus	Nystagmu	ERG
			OD	OS	OD	OS	OD	OS	OD	OS				
F1	3	Male	0.12	0.1	0.3 (-6.50DS/-1.75DC×27°)	0.3 (-8.50DS/-0.75DC×130°)	13	13	27.05	27.83	No	Yes	No	iCSNB ERG
F2	3	Male	0.06	0.06	0.15 (-10.0DS/-2.50DC×23°)	0.15 (-11.0DS/-2.75DC×152°)	12	10	28.26	28.47	No	Yes	No	iCSNB ERG
F3	2	Male	0.12	0.12	0.2 (-6.75DS/-1.25DC×57°)	0.2 (-6.25DS/-0.50DC×64°)	12	11	25.37	25.31	Yes	Yes	Yes	cCSNB ERG
F4	5	Male	0.2	0.2	0.6 (-5.25DS/-1.50DC×87°)	0.6 (-5.25DS/-2.00DC×81°)	19	17	24.48	24.71	Yes	Yes	Yes	cCSNB ERG
F5	5	Female	0.1	0.1	0.4 (-8.00DS/-0.25DC×73°)	0.4 (-7.75DS/-0.75DC×101°)	15	16	25.93	25.87	Yes	Yes	Yes	cCSNB ERG

F: Family; CSNB: Congenital stationary night blindness; iCSNB: Incomplete CSNB; cCSNB: Complete CSNB; UCVA: Uncorrected visual acuity; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; ERG: Electroretinogram; DS: Diopter sphere; DC: Diopter cylinder; OD: Right eye; OS: Left eye.

Table 2 Genetic testing results of probands from five CSNB families

Parameters	F1	F2	F3	F4		F5	
Gene	*CACNA1F*	*CACNA1F*	*NYX*	*TRPM1*	*TRPM1*	*TRPM1*	*TRPM1*
Chromosome	Chr X	Chr X	Chr X	Chr 15	Chr 15	Chr 15	Chr 15
NM_	NM_001256789.3	NM_001256789.3	NM_001378477.3	NM_001252024.2	NM_001252024.2	NM_001252024.2	NM_001252024.2
Nucleotide	c.1873C>T	c.244C>T	c.70_93del	c.2130T>A	c.1089+1G>A	c.2984T>C	c.1089+1G>A
Amino acid	p.Arg625Ter	p.Arg82*	p.Arg24_A31del	p.Tyr710*	-	p.Met995Thr	-
Exon	Exon 14	Exon 2	Exon 3	Exon 18	Exon 9	Exon 23	Exon 9
Source	Mother	Mother	Mother	Father	Mother	Father	Mother
1000g2015aug_all	2.78535e-06	4.55385e-06	5.63980e-06	-	2.00496e-05	-	2.00496e-05
1000g2015aug_eas	-	3.31071e-05	-	-	-	-	-
SIFT_	-	-	-	-	-	D	-
Polyphen2_HVAR_	-	-	-	-	-	D	-
LRT	U	D	-	D	-	D	-
MutationTaster	A	A	-	A	D	D	D
MutationAssessor	-	-	-	-	-	M	-
FATHMM_	-	-	-	-	-	T	-
PROVEAN_	-	-	-	-	-	D	-
CADD_	-	-	1.381367	6.443573	4.78855	3.846281	4.78855
GERP++	2.51	3.11	-	1.43	5.72	5.92	5.72
DANN	0.995	0.998	-	0.996	0.995	0.994	0.995
spliceAI	-	-	-	-	0.99	-	0.99
REVEL_score	-	-	-	-	-	0.875	-
Level	Pathogenic	Pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic
Mutation site	Known	Known	Known	Novel	Known	Novel	Known

CSNB: Congenital stationary night blindness; F: Family.

Table 3 Clinical follow-up records of the proband of Family 1

Date of examination	VA		Refraction		Axial length (mm)		Corneal curvature (D)	
	OD	OS	OD	OS	OD	OS	OD	OS
2016-12-26	N/A	N/A	-5.00DS/-1.25DC×20°	-5.50DS/-0.75DC×118°	N/A	N/A	42.37	41.87
2018-01-14	0.2	0.2	-5.50DS/-1.50DC×30°	-6.00DS/-0.50DC×120°	N/A	N/A	41.99	41.62
2018-09-01	0.2	0.25	-5.50DS/-1.75DC×22°	-6.25DS/-0.75DC×116°	N/A	N/A	42.12	41.62
2019-03-02	N/A	N/A	-5.50DS/-1.50DC×22°	-6.25DS/-0.75DC×117°	N/A	N/A	41.98	42.02
2019-11-01	0.2	0.3	-5.25DS/-1.75DC×20°	-6.50DS/-1.00DC×130°	N/A	N/A	41.96	42.25
2020-04-06	N/A	N/A	-5.50DS/-1.75DC×30°	-6.50DS/-0.75DC×120°	N/A	N/A	N/A	N/A
2021-01-16	0.3	0.3	-5.75DS/-1.50DC×33°	-6.50DS/-1.25DC×116°	N/A	N/A	41.75	41.18
2021-06-21	0.3	0.3	-5.50DS/-1.75DC×24°	-6.50DS/-0.75DC×129°	26.27	26.87	41.50	41.50
2021-12-11	N/A	N/A	-6.00DS/-1.50DC×39°	-6.50DS/-1.00DC×138°	26.39	26.97	N/A	N/A
2022-03-05	0.3	0.25	-5.75DS/-1.75DC×28°	-6.25DS/-0.50DC×127°	26.42	27.07	41.85	41.36
2022-12-17	N/A	N/A	-6.00DS/-1.75DC×26°	-6.50DS/-0.75DC×127°	26.55	27.23	41.65	41.16
2023-02-11	N/A	N/A	-6.25DS/-2.25DC×26°	-7.50DS/-0.75DC×129°	N/A	N/A	41.75	41.16
2023-02-23	0.3	0.25	-6.25DS/-2.00DC×22°	-7.50DS/-1.00DC×130°	N/A	N/A	41.75	41.25
2024-07-04	0.3	0.3	-6.25DS/-2.00DC×25°	-8.00DS/-0.75DC×135°	26.84	27.66	41.99	41.59
2025-01-19	0.3	0.3	-6.50DS/-1.75DC×27°	-8.25DS/-0.75DC×130°	27.05	27.83	41.86	41.51

VA: Visual acuity; N/A: Not available; OD: Right eye; OS: Left eye; DS: Diopter sphere; DC: Diopter cylinder.

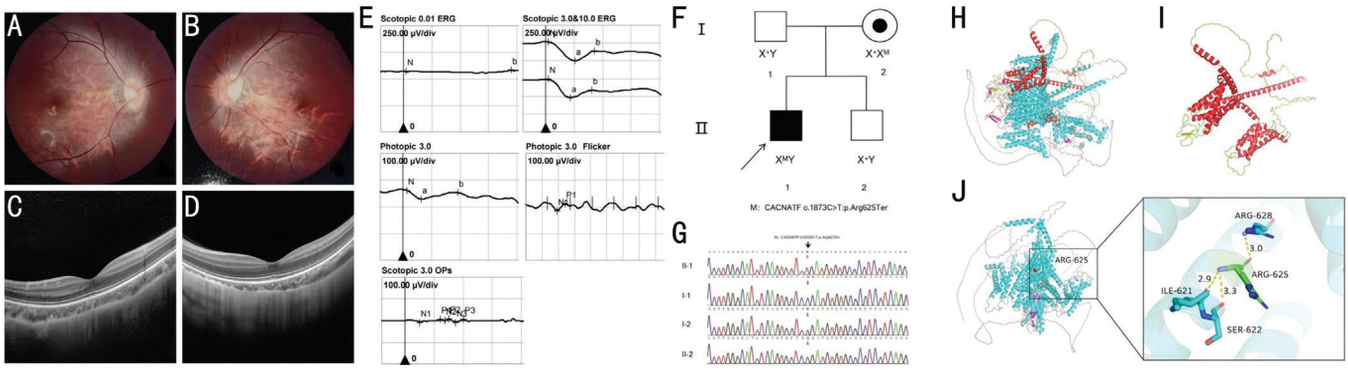

Figure 1 Clinical manifestations and genetic testing results in F1 proband A, B: Fundus alterations in both eyes associated with myopia; C, D: Normal morphological characteristics of the fovea in both eyes; E: iCSNB ERG; F: Tree of Family; G: Sanger sequencing indicated that the proband and his mother harbored the *CACNA1F* gene c.1873C>T (p.Arg625Ter) mutation; H: Alignment of the protein structures of wild-type CACNA1F (blue) and mutant p.R625ter (red); I: Protein structure of the mutant p.Arg625Ter; J: Polar arginine structure at position 625 in the wild-type protein. iCSNB: Incomplete congenital stationary night blindness; ERG: Electroretinogram.

CSNB cases[10]. This variant leads to the complete loss of gene products and a reduction in normal protein levels (PVS1_ Very Strong). It is absent from population databases (PM2) and has been detected multiple times in CSNB patients (PS4). Computational evidence corroborates a deleterious effect (PP3), and the patient's phenotype is specific to CSNB with a single-genetic etiology (PP4). Therefore, according to ACMG, it is classified as pathogenic (PVS1+PS4+PM2+PP3+PP4).

In F2, the proband was a 7-year-old male who had presented with bilateral visual impairment and photophobia symptoms for 4y, without a prior history of night blindness. At the age of 3y, he was misdiagnosed with bilateral high myopia and amblyopia. The clinical manifestations and genetic testing results of the patient are presented in detail in Figure 2. The patient was finally diagnosed with iCSNB accompanied by eoHM. Whole-exome sequencing detected a hemizygous nonsense variant, c.244C>T (p.Arg82Ter), within the *CACNA1F* gene. Sanger sequencing revealed that the mother harbored the identical heterozygous variant. This nonsense variant introduces a premature termination codon, is predicted to undergo nonsense-mediated decay, leads to the complete loss of gene products, and results in a reduction in normal protein levels (PVS1). The variant is absent from population databases (PM2: gnomAD frequency=0) and has been detected multiple times in patients with CSNB (PS4)[11]. Computational evidence indicates a deleterious effect (PP3), and the patient's phenotype is specific to CSNB with a single-genetic etiology (PP4). Therefore, according to the ACMG classification, this variant is categorized as pathogenic (PVS1+PS4+PM2+PP3+PP4).

In F3, the proband was a 4-year-old male who had suffered from bilateral night blindness since childhood, and there was a family history of consanguineous marriage. The patient presented with symptoms of night blindness from an early age and was previously misdiagnosed with bilateral high myopia, amblyopia, and strabismus, and had undergone spectacle correction. The clinical manifestations and genetic testing results of the patient are depicted in Figure 3. The final diagnosis was cCSNB accompanied by eoHM. Whole-exome sequencing identified a hemizygous in-frame deletion variant, c.70_93del (p.Arg24_Ala31del), within the *NYX* gene. The proband's mother harbors the identical heterozygous variant, presenting a normal clinical phenotype. Meanwhile, the proband's maternal grandfather also tests positive for this same heterozygous variant, manifesting clinical symptoms analogous to those of the proband. The deletion of amino acids may disrupt protein function as a result of alterations in length. This in-frame deletion is regarded as moderate evidence within the ACMG Pathogenicity Classification. The in-frame deletion c.70_93del (p.Arg24_Ala31del) satisfies the criteria for likely pathogenicity based on the following aspects: robust case-control data (PS4: reported in multiple affected individuals), moderate functional influence (PM4: a 24-bp deletion predicted to cause protein elongation), and abnormality (PP4). The variant is absent from population databases (PM2: gnomAD frequency=0) and has been detected multiple times in patients with CSNB (PS4)[12]. Multiple computational evidences corroborate a deleterious effect (PP3), and the patient's phenotype is highly specific for CSNB with a single genetic etiology (PP4). Literature reports suggest that this variation is associated with the disease in multiple congenital stationary night blindness patient families (PP1). Consequently, in accordance with the ACMG variant classification, this variant is classified as likely pathogenic (PS4+PM2+PM4+PP3+PP4+PP1).

In F4, the proband was a six-year-old male. The medical history indicated that the proband had been misdiagnosed with bilateral high myopia complicated by amblyopia at another hospital six months prior. By that time, he had already initiated

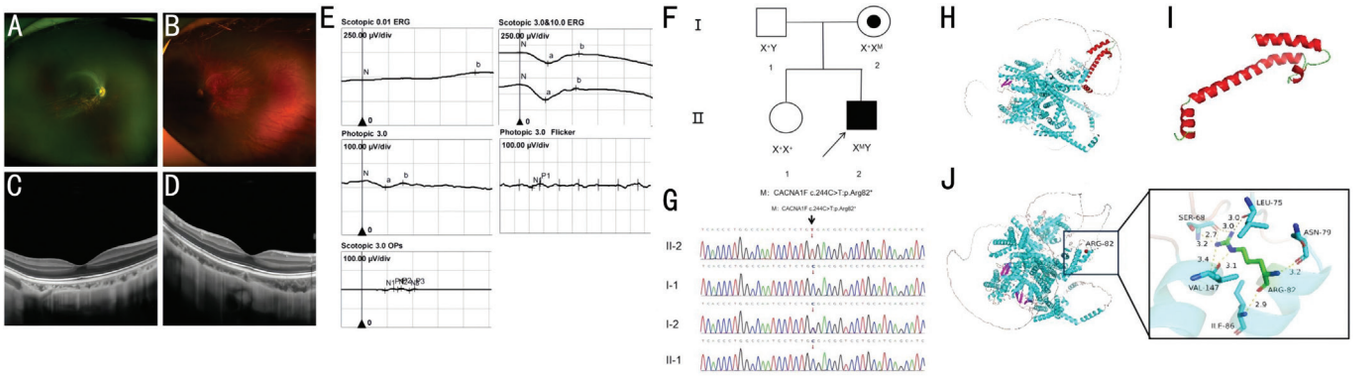

Figure 2 Clinical manifestations and genetic testing results in F2 proband A, B: Bilateral alterations in the myopic fundus; C, D: Normal bilateral foveal morphologies; E: iCSNB ERG; F: Tree of Family; G: Sanger sequencing results demonstrated that both the proband and his mother carried the nonsense variant c.244C>T (p.Arg82*) in the *CACNA1F* gene; H: Comparison of the protein architectures between the wild-type CACNA1F (blue) and the variant p.Arg82* (red); I: Protein architecture of the mutant p.Arg82*; J: Structure of the polar arginine at position 82 of the wild-type CACNA1F. iCSNB: Incomplete congenital stationary night blindness; ERG: Electroretinogram.

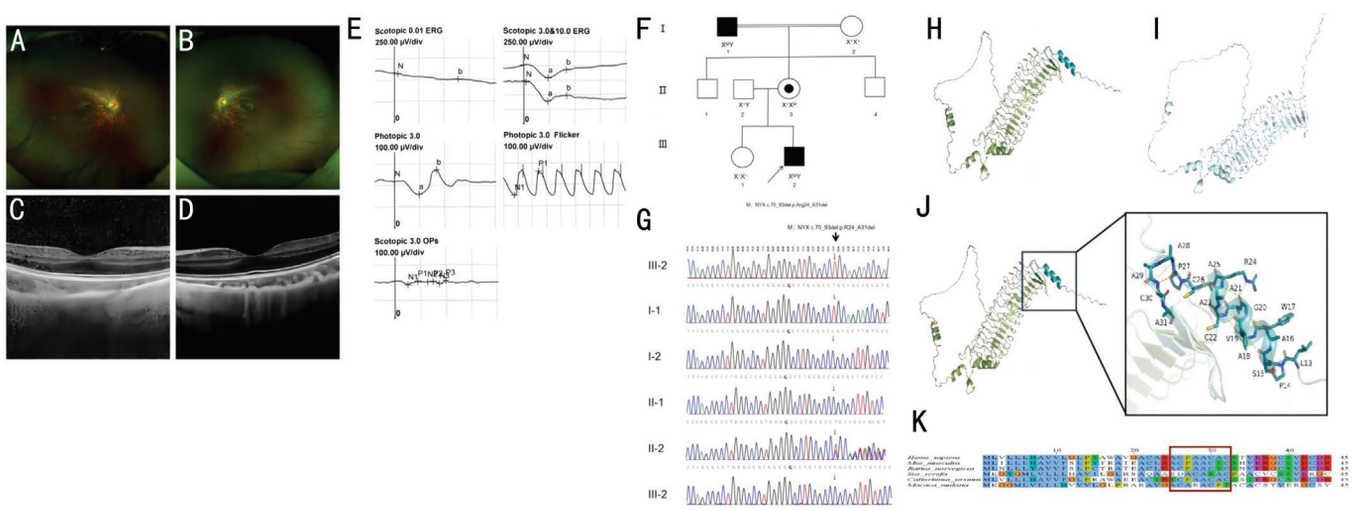

Figure 3 Clinical manifestations and genetic testing results in F3 proband A, B: Fundus alterations in both eyes associated with myopia; C, D: Normal morphological characteristics of the fovea in both eyes; E: cCSNB ERG; F: Tree of Family; G: Gene sequencing profile: The patient, the mother, and the maternal grandfather all harbor the *NYX* gene c.70_93del (p.Arg24_Ala31del) mutation; H: Structure of the wild-type NYX; I: Structure of the mutant p.Arg24_Ala31del (represented in sky blue); J: Comparison between the wild-type NYX (depicted in green) and the mutant p.Arg24_Ala31del structure (in sky blue); K: Amino acid sequence at variant site was compared with homologous protein sequences of multiple species (amino acid at variant site was highly conserved). cCSNB: Complete congenital stationary night blindness; ERG: Electroretinogram.

the use of corrective lenses and undergone amblyopia training. The patient's clinical manifestations and genetic testing results are presented in detail in Figure 4. The final diagnosis was cCSNB complicated by eoHM. Whole-exome sequencing detected compound heterozygous variants in *TRPM1*, namely c.2130T>A (p.Tyr710*) and c.1089+1G>A. Both variants were absent from population databases (PM2) and were non-functional variants with a loss-of-function (LOF) pathogenic mechanism (PVS1), which was supported by multiple computational evidence. The variant exerted a deleterious impact on the gene or gene product (PP3), and the patient's phenotype was highly specific for CSNB with a single genetic etiology (PP4). These variants co-segregated with the disease within the family (PP1). Therefore, in accordance with the ACMG variant classification, this variant is classified as pathogenic (PVS1+PM2+PP3+PP4+PP1).

In F5, the proband was a 6-year-old female who had been wearing glasses for one year with suboptimal visual acuity correction. Her medical history indicated persistent clinical symptoms of orientation impairment in dark environments since childhood. Moreover, the patient had previously been misdiagnosed with bilateral high myopia complicated by amblyopia at another medical institution. The patient's clinical manifestations and genetic testing results are presented in detail in Figure 5. The final diagnosis was cCSNB complicated by eoHM. Whole-exome sequencing detected compound

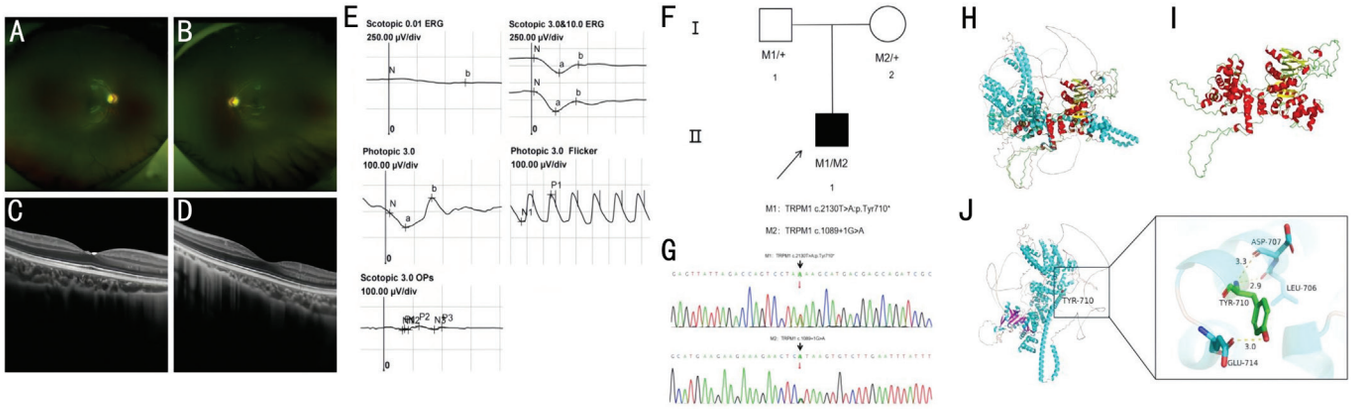

Figure 4 Clinical manifestations and genetic testing results in F4 proband A, B: Fundus alterations in both eyes associated with myopia; C, D: Normal morphological characteristics of the fovea in both eyes; E: cCSNB ERG; F: Tree of Family; G: Gene sequencing outcomes: The patient harbors a compound heterozygous mutation in the *TRPM1* gene: c.2130T>A (p.Tyr710*), a nonsense mutation; c.1089+1G>A, a splice-site mutation; H: Comparison of protein architectures between wild-type TRPM1 (blue) and the mutant p.Tyr710* (red); I: Protein architecture of the mutant p.Tyr710*; J: Structure of the wild-type tyrosine (Y710) residue. cCSNB: Complete congenital stationary night blindness; ERG: Electroretinogram.

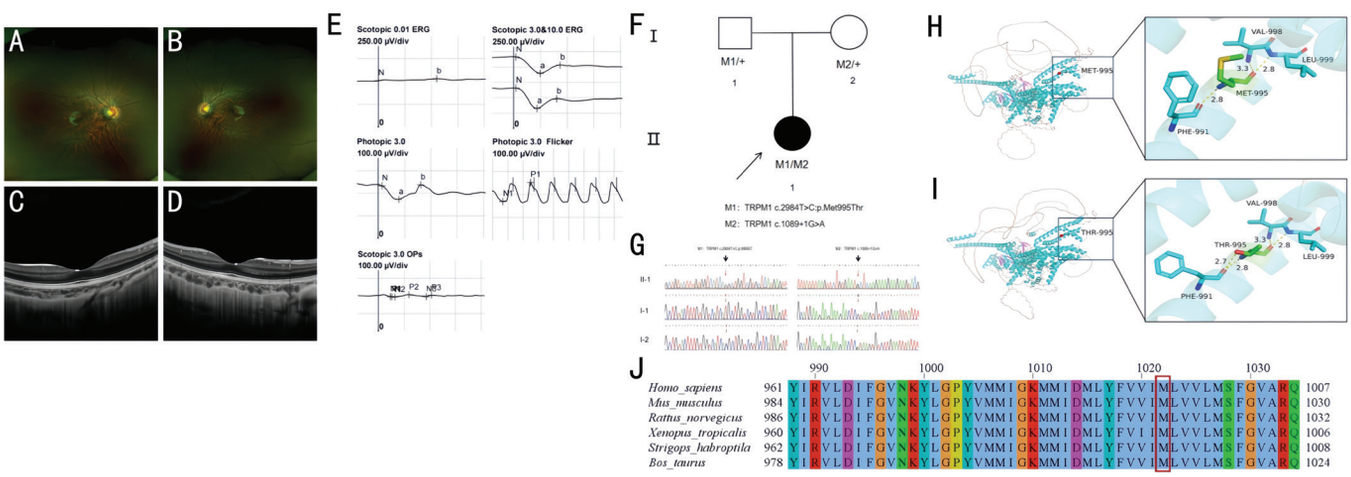

Figure 5 Clinical manifestations and genetic testing results in F5 proband A, B: Fundus alterations in both eyes associated with myopia; C, D: Normal morphological characteristics of the fovea in both eyes; E: cCSNB ERG; F: Tree of Family; G: Sanger sequencing chromatogram indicating that the subjects harbor compound heterozygous variants in the *TRPM1* gene: c.2984T>C (p.Met995Thr) and c.1089+1G>A. The c.2984T>C (p.Met995Thr) variant is derived from the father, whereas the c.1089+1G>A variant is derived from the mother. H: Structural configuration of the wild-type TRPM1 protein; I: Structural configuration of the mutant p.Met995Thr protein; J: Comparison of the amino acid sequence at the variant site with homologous protein sequences of multiple species (the amino acid at the variant site exhibited a high degree of conservation). cCSNB: Complete congenital stationary night blindness; ERG: Electroretinogram.

heterozygous variants in *TRPM1*, specifically c.2984T>C (p.Met995Thr) and c.1089+1G>A. The missense variant p.Met995Thr is not present in population databases (PM2: gnomAD frequency=0), and computational analysis provides evidence suggesting a deleterious effect (PP3). The patient's phenotype is highly characteristic of CSNB with a single genetic etiology (PP4). CSNB exhibits AR inheritance. The proband harbors a suspected pathogenic variant in the trans position relative to p.Met995Thr (PM3). Consequently, according to the ACMG variant classification, this variant is categorized as likely pathogenic (PM3+PM2+PP3+PP4). The variant c.1089+1G>A represents a classic splicing alteration associated with an LOF disorder. The transcript containing this variation is biologically relevant, not located in the last or second-last coding exon within the final 50 base pairs, and may trigger nonsense-mediated mRNA decay, thereby influencing the function of the encoded protein. The Splice AI prediction score is ≥0.5, thus justifying the use of PVS1 evidence. This splice variant is absent from population databases (PM2). Therefore, in line with the ACMG variant classification, this variant is classified as likely pathogenic (PVS1+PM2+PP3).

Literature Review Through a systematic literature review, a total of 14 studies[13-26] were incorporated, encompassing

Table 4 Literature review on clinical phenotypes of CSNB patients associated with *CACNA1F*, *NYX*, and *TRPM1* genes

Gene	Mutation	Protein	Country	Sex	Age	Refraction		VA		Nyctalopia	Nystagmu	Strabismus	ERG	References
						OD	OS	OD	OS					
CACNA1F	c.2436_2437delGGinsCT	p.Glu812Aspfs*2	Saudi Arabia	Male	7	+5.00	+4.75	0.2	0.2	Yes	Yes	No	iCSNB ERG	13
CACNA1F	c.3401G>A	-	Saudi Arabia	Male	7	N/A	+3	HM	0.15	Yes	Yes	Yes	iCSNB ERG	13
CACNA1F	c.1301C>T	p.Ala434Val	Republic of Korea	Male	3	-1.0	0	0.9	0.8	N/A	Yes	Yes	iCSNB ERG	14
CACNA1F	c.2175_2179delins27	p.Gly726Ilefs*61	Republic of Korea	Male	3	0.5	1.0	0.7	0.7	N/A	Yes	Yes	iCSNB ERG	14
CACNA1F	c.1910+1G>A	-	Republic of Korea	Male	3	-1.00	-1.50	0.8	0.8	N/A	Yes	No	iCSNB ERG	14
CACNA1F	c.4049G>A	p.Gly1350Asp	Republic of Korea	Male	3	-10.5	-9.5	0.7	0.6	N/A	No	Yes	iCSNB ERG	14
CACNA1F	c.342delC	p.Phe115Serfs*22	Republic of Korea	Male	4	-11.50	-10.00	0.6	0.6	N/A	Yes	No	iCSNB ERG	14
CACNA1F	c.2914C>T	p.Arg972*	Republic of Korea	Male	4	-3.00	-3.00	0.6	0.6	N/A	No	Yes	iCSNB ERG	14
CACNA1F	c.2576+1G>A	-	Republic of Korea	Male	7	-9.50	-8.50	0.6	0.6	N/A	Yes	No	iCSNB ERG	14
CACNA1F	c.5156G >C	p.Arg1719Thr	Italy	Male	9	-2.75	-3.50	0.9	0.9	No	No	No	iCSNB ERG	15
CACNA1F	c.4294-11C>G	-	the U.K.	Male	13	-7.50	-7.50	0.5	0.5	Yes	Yes	No	iCSNB ERG	16
CACNA1F	c.3825+1G> A	-	Pakistan	Female	7	-12.00	-11.50	0.15	0.2	No	Yes	Yes	iCSNB ERG	17
NYX	c.339_353delTGAGCTGCGCCTGGC	p.Glu114_Ala118del	the U.S.	Male	3	-6.25	-6.25	0.16	0.1	Yes	Yes	Yes	cCSNB ERG	18
NYX	c.626G>C	p. Arg209Pro	China	Male	9	-9.00	-10.00	0.3	0.2	Yes	Yes	No	cCSNB ERG	19
NYX	c.121delG	p.Glu41fs*100	China	Female	31	-16.00	-9.00	0.2	0.4	Yes	Yes	No	cCSNB ERG	19
NYX	c.182_183insT	p.Cys62Valfs * 53	Korea	Male	3	-6.50	-5.50	N/A	N/A	N/A	Yes	No	cCSNB ERG	14
NYX	c.38-1_ 38delGCinsTT	-	Korea	Male	5	-9.50	-9.50	0.6	0.6	N/A	No	Yes	cCSNB ERG	14
NYX	c.281G>C	p.Arg94Pro	China	Male	11	-9.50	-9.25	0.5	0.5	Yes	No	No	cCSNB ERG	20
NYX	c.302T > C	p.Ile101Thr	China	Male	4	-6.00	-6.00	N/A	N/A	Yes	No	No	cCSNB ERG	20
NYX	c.283delC	p.His95fs	Russia	Male	6	-6.00	-6.00	0.1	0.3	Yes	No	No	cCSNB ERG	21
NYX	c.647A>T	p.Asn216I	China	Male	6	-9.00	-9.00	0.8	0.8	Yes	No	No	cCSNB ERG	22
TRPM1	c.2594C>T	p.Ala865Val	China	Female	6	-7.00	-7.25	0.6	0.6	Yes	No	No	cCSNB ERG	23
	c.6693_669 6delaagt	-												
TRPM1	c.3262G>A	p.Ala1088Thr	China	Male	3	-5.75	-5.50	0.3	0.3	Yes	No	Yes	cCSNB ERG	23
	c.3250T>C	P.cys1084Arg												
TRPM1	c.3280C>T	p.Arg1094*	Republic of Korea	Male	19	-7.50	-6.50	0.3	0.3	N/A	No	No	cCSNB ERG	14
	c.3794delA	p.Asn1265Ilefs*42												
TRPM1	c.215A>G	p.Tyr72C	the U.S.	N/A	9	-9.00	-8.00	1.0	1.0	Yes	No	No	cCSNB ERG	24
	c.215A>G	p.Tyr72C												
TRPM1	c.1023+1G>A	-	the U.S.	N/A	15	-4.00	-4.25	1.0	1.0	Yes	Yes	No	cCSNB ERG	24
	c.1406 t >C	p.Leu469S												
TRPM1	c.1023+1G>A	-	the U.S.	N/A	14	-5.50	-6.50	0.5	0.3	Yes	No	Yes	cCSNB ERG	24
	c.1406 t >C	p.Leu469S												
TRPM1	c.296T>C	p.L99P	the U.S.	N/A	9	-6.50	-6.00	0.25	0.3	Yes	Yes	Yes	cCSNB ERG	24
	c.2597-2599del	p.Ser866del												
TRPM1	c.2894A>C	p.D965A	the U.S.	N/A	15	-13.50	-14.00	1.0	1.0	Yes	No	Yes	cCSNB ERG	24
	Deletion of exon 2-7	No functional protein												
TRPM1	c.1871G>A	p.R624H	the U.S.	N/A	10	-9.00	-10.25	0.2	0.4	Yes	Yes	Yes	cCSNB ERG	24
	Undefined large deletion encompassing *TRPM1*	Lack of protein												
TRPM1	c.215A>G	p.Tyr72C	the U.S.	N/A	11	-13.75	-14.00	0.8	1.0	Yes	No	Yes	cCSNB ERG	24
	c.215A>G	p.Tyr72C												

N/A: Not available; VA: Visual acuity; HM: Hand move; OD: Right eye; OS: Left eye; CSNB: Congenital stationary night blindness; iCSNB: Incomplete CSNB; cCSNB: Complete CSNB; ERG: Electroretinogram.

Table 5 Clinical features by CSNB subtype and genotype

Clinical feature	All cCSNB		*NYX*		*TRPM1*		All iCSNB		*CACNA1F*		References
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	
Nyctalopia	100	33/33	100	19/19	100	8/8	54	31/57	58	29/50	25
	66	41/62	64	16/25	71	15/21	63	38/60	64	38/59	26
Nystagmu	72	28/39	65	13/20	80	8/10	66	41/62	65	36/55	25
	44	27/62	44	11/25	33	7/21	60	36/60	59	35/59	26
Strabismus	59	22/37	45	9/20	70	7/10	38	23/61	39	21/54	25
	32	20/62	40	10/25	33	7/21	20	12/60	20	12/59	26
Photophobia	21	7/33	26	5/19	20	2/10	53	31/59	50	26/52	25
	3	2/62	4	1/25	0	0/21	10	6/60	10	6/59	26
Color defect	14	4/28	27	4/15	0	0/7	47	25/53	46	21/46	25
	18	2/11	29	2/7	0	0/3	33	6/18	33	6/18	26

CSNB: Congenital stationary night blindness; iCSNB: Incomplete CSNB; cCSNB: Complete CSNB.

reports from China, Saudi Arabia, Republic of Korea, Italy, the United Kingdom, the United States, Russia, Pakistan, and the Netherlands (Tables 4 and 5). The incidence of CSNB exhibited substantial variation across diverse regions and ethnic groups. Nevertheless, the types of causative genes remained constant, with the *CACNA1F* and *NYX* genes being the most prevalent, accounting for over 50% of the cases, followed by the *TRPM1* gene.

Table 4 comprised a total of 31 patients diagnosed with CSNB through genetic testing. The pathogenic genes were consistent with those identified in this study, specifically *CACNA1F* (12 cases), *NYX* (9 cases), and *TRPM1* (10 cases), with the aim of facilitating a more comprehensive comparison of the relationship between genotype and clinical phenotype. Among patients with *CACNA1F* mutations, the refractive errors demonstrated the widest range, spanning from +5 to -14 D, including hyperopia and high myopia. Moreover, it was observed that the higher the degree of genetic variation, the greater the likelihood of patients presenting with myopia. Approximately 40% of the *CACNA1F* cases did not report symptoms of night blindness, and only one patient exhibited neither nystagmus nor strabismus.

Patients with *NYX* and *TRPM1* mutations all presented with moderate to high myopia (-4 to -16 D). The average SE was approximately -6.5 D in the *NYX* group and -7.4 D in the *TRPM1* group. No hyperopic cases were reported in either group, and all patients had a history of congenital night blindness. Electrophysiological findings indicated markedly reduced dark-adapted ERG responses in all three groups. Under light-adapted conditions, the *CACNA1F* group showed more severe ERG impairment, while the *NYX* and *TRPM1* groups displayed normal to mildly or moderately reduced responses.

In accordance with the multi-center study conducted by Bijveld *et al*[25], which encompassed 101 Dutch patients with CSNB, all patients diagnosed with cCSNB reported experiencing nyctalopia, while merely 54% of patients with iCSNB reported such symptoms. Photophobia and color vision defects were more prevalent in iCSNB, while nystagmus and strabismus were frequently observed in both forms. The study also confirmed a significant difference in refractive error between cCSNB and iCSNB patients (median -7.4 *vs* -4.8 D), which is highly consistent with the findings of the present study. Furthermore, Katta *et al*[26], in a report on 122 CSNB patients, revealed that iCSNB patients exhibited more severe color vision impairment, whereas *TRPM1*- and *NYX*-related cCSNB patients presented with high myopia from birth, with a significantly faster progression of myopia compared to *CACNA1F*-related iCSNB patients.

DISCUSSION

In recent years, clinical practice has revealed that eoHM frequently serves as the primary impetus for ophthalmic consultations among patients with inherited ocular diseases. In the present study, a combined approach of electrophysiological and genetic testing was conducted on 42 eoHM families, uncovering a complex etiological spectrum contributing to the diminished best-corrected visual acuity in eoHM patients. Among them, five patients were diagnosed with CSNB. These patients manifested at an early age, all presenting with reduced BCVA and eoHM, with or without symptoms of night blindness. Fundus examinations yielded unremarkable results, and all had been previously misdiagnosed with amblyopia, showing no improvement following amblyopia training. Genetic testing identified variants in the *CACNA1F*, *NYX*, and *TRPM1* genes in the five probands. Based on electrophysiological findings and clinical features, a definitive diagnosis of CSNB was established.

The primary distinction between cCSNB and iCSNB resides in the mechanism through which the pathogenic gene impacts the ON and OFF bipolar cell pathways[27-28]. In cCSNB, encoded proteins are in the postsynaptic dendrites of ON bipolar cells, causing ON pathway dysfunction, so cCSNB is also an ON bipolar cell dysfunction disorder. On the contrary, genes related to iCSNB encode proteins in the presynaptic terminals of photoreceptors, disrupting glutamate release and leading to impairment in both ON and OFF pathways[25]. As a result, iCSNB patients usually have more severe cone dysfunction, showing color vision defects and photophobia, while cCSNB is mainly characterized by night blindness and high myopia. The strong correlation between CSNB and myopia has drawn much academic attention, with CSNB seen as an ideal model for studying myopic pathogenesis and treatment[26]. However, unlike “school-age myopia”, CSNB-associated myopia progresses rapidly before 4y, then the progression rate slows to about 0.12 D per year on average, and there are no more changes after 15 years old[29]. Very recently, a comparable study was published by Igelman *et al*[30] about the natural history of myopic progression in patients with CSNB. They found that in 78 patients with CSNB, myopia continued to progress between the ages of 0 and 18y at rates of -0.25, -0.26, and -0.33 D per year for genotypes *CACNA1F*, *NYX*, and *TRPM1*, respectively. However, they assumed a linear trend for the natural course of the refraction. In this study, the F1 proband was initially diagnosed with bilateral high myopia at the age of 3y. During the 9-year follow-up period (Table 3), the progression rates of myopia in the right and left eyes were -0.19 D per year and -0.31 D per year, respectively. These rates were significantly lower than those of “school-age myopia”, and the underlying reason is the difference in pathogenic mechanisms. The patient was misdiagnosed with amblyopia for an extended period and underwent amblyopia training therapy, but no improvement in visual acuity was attained. Consequently, comprehensive clinical evaluations, including ERG testing and genetic testing, should be routinely performed on patients with eoHM to exclude the possibility of CSNB.

cCSNB is associated with mutations in the genes *NYX*, *TRPM1*, *GRM6*, *GPR179*, *LRIT3*, and *EGFLAM*. iCSNB is caused by mutations in the genes *CACNA1F*, *CABP4*,

and *PDE6B*[9,31]. A recent study reported a novel pathogenic gene for iCSNB, *RIMS2*, the mutations of which can lead to a syndromic iCSNB phenotype accompanied by neurodevelopmental abnormalities and pancreatic involvement[32]. Among these genes associated with CSNB, the most frequently mutated genes are *CACNA1F* and *NYX* (collectively accounting for over 50% of cases), followed by *TRPM1*. In 2000, Bech-Hansen *et al*[33] identified mutations in the *CACNA1F* gene in patients with incomplete X-linked CSNB, thus establishing *CACNA1F* as the first causative gene for X-linked CSNB. *CACNA1F* (Xp11.23), spanning 28 kb across 48 exons, encodes the 1977-amino acid Cav1.4 α1 subunit of L-type voltage-gated Ca^{2+} channels. Expressed in the retina's outer nuclear, inner nuclear, and ganglion cell layers, Cav1.4 mediates Ca^{2+}-dependent tonic glutamate release from photoreceptors[32-33]. LOF mutations abrogate Ca^{2+} influx, arresting photoreceptor synaptic ribbon maturation, disrupting photoreceptor-bipolar cell signal transmission, and inducing aberrant synaptic sprouting. These pathological changes drive progressive cone degeneration, underlying the combined phenotype of iCSNB with myopia[34]. In this study, F1 and F2 carried hemizygous variants in the *CACNA1F* gene: a nonsense mutation c.1873C>T (p.R625Ter) and a hemizygous nonsense variant c.244C>T (p.Arg82*), respectively. These variants cause structural defects in the encoded protein, resulting in a complete loss of protein function. Individuals with *CACNA1F*-related iCSNB usually show nystagmus, photophobia, nyctalopia, and vision impairments, along with myopic refractive errors. Fundus is generally normal except for high-myopia characteristics[35-36]. F1 and F2 had high myopia with strabismus, no nystagmus or night-blindness history. Fundus examinations were unremarkable, leading to long-term misdiagnosis. ERG findings suggest ON and OFF response abnormalities, consistent with the *CACNA1F* mutation. Based on electrophysiological results and genetic testing, both probands were diagnosed with bilateral iCSNB accompanied by eoHM. The inheritance is X-linked recessive. Cone photoreceptors form synaptic connections involving both ON and OFF bipolar cells, while rod photoreceptors only connect to ON bipolar cells. Integrating ERG findings and clinical phenotypes helps localize gene mutations and signaling pathways, improving disease diagnosis and classification accuracy.

Apart from the *CACNA1F* gene, the *NYX* gene is another well-known causative gene for X-linked CSNB[31]. In the year 2000, Pusch *et al*[37] initially identified and designated the *NYX* gene within 24 families with Schubert-Bornschein type of CSNB. *NYX* (Xp11.4), spanning 2.7 kb across 3 exons, encodes the 481-amino acid leucine-rich repeat proteoglycan nyctalopin. Expressed in retinal bipolar and ganglion cells, it stabilizes the mGluR6-*TRPM1* complex on ON bipolar cells to facilitate photoreceptor signal transmission[38]. LOF mutations impair ON-pathway signaling, reduce retinal dopamine levels, and are linked to high myopia in animal models and humans[39]. Genetic testing was conducted on the proband of the F3 pedigree, and the structural model (Figure 3J) offered substantial evidence. The p.Arg24_Ala31del mutation significantly disrupted the local three-dimensional structure of the protein by entirely eliminating a stable structural loop, ultimately resulting in the loss of protein function. Considering the young age of the proband and the limited compliance, certain clinical examinations were not accomplished. Nevertheless, the ERG results demonstrated characteristic manifestations. Based on the clinical presentation and genetic test outcomes, the proband was diagnosed with cCSNB associated with eoHM. The maternal grandfather in this family harbored the same *NYX* gene variant and was afflicted with high myopia and night blindness, whereas the heterozygous mother exhibited no clinical aberrations. The co-phenotypic segregation of genotypes and phenotypes in this family corroborates an X-linked recessive inheritance pattern.

In 2009, Li *et al*[40] conducted an analysis of the *TRPM1* gene in 10 pedigrees of AR Schubert-Bornschein type of CSNB and identified 3 pedigrees harboring mutations in the *TRPM1* gene. *TRPM1* (15q13-q14) encodes a 1603-amino acid TRP channel protein, the most common cause of autosomal recessive cCSNB[41]. Expressed in retinal ON bipolar cells, it regulates intracellular Ca^{2+} homeostasis critical for signal transduction[42]. Biallelic mutations induce inner retinal structural alterations, reduce amacrine cell-derived dopamine (a key myopia modulator), and drive the cCSNB-eoHM phenotype[42-45]. The F4 and F5 families presented with night blindness symptoms from early childhood, accompanied by moderate visual impairment, eoHM, nystagmus, and strabismus, yet without photophobia or color vision deficiencies. These families were misdiagnosed as having amblyopia for an extended period. Comprehensive ERG examinations of the family members disclosed characteristic alterations consistent with cCSNB. Genetic testing indicated that both probands harbored a compound heterozygous mutation in the *TRPM1* gene, with a genotype-phenotype segregation pattern conforming to an autosomal recessive inheritance model. Based on electrophysiological findings and genetic testing outcomes, the F4 and F5 families were diagnosed with cCSNB associated with eoHM.

A recent domestic cohort study on pediatric CSNB reported a 91.53% male predominance, with reduced visual acuity, strabismus, and nyctalopia as primary parental concerns[9]. BCVA was significantly better in cCSNB (median 20/40) than iCSNB (median 20/63), and iCSNB (especially *CACNA1F*-

related cases) exhibits greater phenotypic heterogeneity, often with minimal or no night blindness[46]. A large Dutch cohort[25] showed cCSNB is dominated by rod-related deficits (100% with night blindness), while iCSNB involves more cone-related abnormalities (53% with photophobia *vs* 21% in cCSNB). Refractive errors in iCSNB range from myopia to hyperopia (16% hyperopic), whereas all cCSNB patients are myopic[25,29]; CABP4-related iCSNB tends to be highly hyperopic, while *CACNA1F* mutations induce myopia[34]. A recent study validates the disparities in final refraction between patients with cCSNB (mean -7.5 D) and patients with iCSNB (mean -5.1 D), and this difference is statistically significant. This disparity might be attributed to a more rapid myopization rate and/or a higher myopic baseline in patients with cCSNB compared to those with iCSNB[29]. In this study, five CSNB patients (four males, one female) with eoHM were included. F1 and F2 had iCSNB due to *CACNA1F* mutations, with visual impairment and strabismus, no nystagmus or night blindness, and F2 also had photophobia. Their light-adapted 3.0 b-wave amplitudes were significantly reduced. F3, F4, and F5 had cCSNB caused by *NYX* and *TRPM1* mutations, with congenital night blindness, nystagmus, and strabismus, and their dark-adapted 0.01 responses were extinguished, typical of cCSNB. cCSNB due to *TRPM1* and *NYX* mutations has earlier, more severe, and faster-progressing myopia, while iCSNB linked to *CACNA1F* mutations has a milder phenotype. Despite the limited sample size, these findings support the correlation between genotype and ERG phenotype.

In conclusion, children with normal fundus in CSNB frequently lack distinct clinical manifestations, which often results in misdiagnosis or missed diagnosis. These children generally display no remarkable ocular structural abnormalities and are commonly accompanied by refractive errors, which are frequently misdiagnosed as amblyopia. As a result, they undergo unnecessary amblyopia training, thereby imposing additional financial burdens on families. Therefore, for children with congenital high myopia or suboptimal corrected visual acuity, apart from routine ophthalmic examinations, ERG should be conducted. Genetic testing may be required to confirm the diagnosis and classify the condition, facilitating the formulation of personalized treatment plans, genetic counseling, and long-term follow-up strategies. This approach is aimed at enhancing the quality of life of affected children and providing families with evidence-based treatment and reproductive guidance.

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