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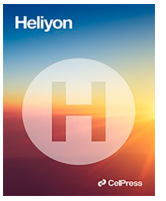

Research article

Compound heterozygous mutations in *GRM6* causing complete Schubert-Bornschein type congenital stationary night blindness

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ABSTRACT

Background: To explore the genetic defects of a Chinese family with complete Schubert-Bornschein type congenital stationary night blindness (CSNB).
Methods: A Chinese family with complete Schubert-Bornschein type CSNB was enrolled in this study. The detailed ocular presentations of the patient were recorded. Targeted gene sequencing including 156 genes related to retinal diseases was used to detect the gene mutation. Sanger sequencing was performed to validate the potential pathogenic variants, and segregation analysis was performed on all available family members. Bioinformatics analysis was performed to predict the impact of the mutations.
Results: By targeted gene sequencing and Sanger sequencing, we identified compound heterozygous mutations in *GRM6*: c.152G>T (p.Gly51Val) and c.727delG (p.Val243SerfsX21). Segregation analysis demonstrated that the mother of the proband carried the missense mutation (c.152G>T) while her father carried the frameshift mutation (c.727delG), indicating CSNB was autosomal recessively inherited in this family. Several bioinformatics prediction programs revealed the mutations were "Damaging" or "Disease Causing" and conservation analysis showed both the codons Gly51 and Val243 were highly conserved among species, suggesting the changes were pathogenic.
Conclusion: By targeted gene sequencing and Sanger sequencing, we detected compound heterozygous mutations (c.152G>T, p.Gly51Val and c.727delG, p.Val243SerfsX21) in *GRM6*. The mutations co-segregated with the phenotype of the family members and are considered to be responsible for complete Schubert-Bornschein type CSNB. However, functional experiments in the future are needed to confirm the pathogenicity of the variants and to elucidate their exact molecular mechanisms causing CSNB.

1. Introduction

Congenital stationary night blindness (CSNB) is a group of clinically and genetically heterogeneous, mainly non-progressive

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hereditary retinal disorders, which are characterized by dysfunction of the phototransduction cascade, signal transmission defect from the photoreceptors to the bipolar cells or defective retinoid recycling in the retinal pigment epithelium (RPE) [1]. Clinical symptoms of CSNB are mainly impaired night vision or poor adaption to darkness, and other manifestations, such as poor visual acuity, myopia, photophobia, nystagmus, strabismus, and fundus abnormalities can also occur [2]. Based on full-field electroretinogram (ERG), patients of CSNB with normal fundi can be distinguished into two types, the Riggs type [3] and the Schubert-Bornschein type [4]. The Riggs type, which is infrequent, features decreased a-wave amplitude in the scotopic bright flash ERG, indicating a defect in the rod photoreceptor [3]. Generally, the phenotype of Riggs type is relatively mild, including night blindness but no high myopia, no nystagmus and normal photopic visual acuity. The Schubert-Bornschein type is further divided into complete CSNB (cCSNB) and incomplete CSNB (icCSNB). cCSNB is caused by dysfunction in the ON bipolar pathway. There is no detectable ERG to a scotopic dim flash and there is an electronegative scotopic bright flash ERG with a normal a-wave and severely reduced b-wave in cCSNB. Patients with cCSNB typically have a history of congenital night blindness, decreased visual acuity, moderate to high myopia, strabismus and nystagmus. Colour vision and visual fields are usually not affected and the fundus appearance is usually normal other than myopic changes [2]. icCSNB is associated with dysfunction in both ON and OFF pathways. The scotopic dim flash ERG is present in icCSNB but of subnormal amplitude and there is a normal a-wave in the scotopic bright flash ERG [2]. The phenotype of icCSNB is more heterogeneous than cCSNB. The patients with icCSNB may present with little or no light vision disturbances, variable degree of refractive error from myopia to hyperopia, various degree of nystagmus and strabismus. Visual fields and fundus appearance are normal in icCSNB while colour vision may show variable defects and visual acuity is lower than in cCSNB [2]. Cone responses are typically less affected than the rod responses, in all forms of CSNB.

The most common inheritance pattern of CSNB is X-linked, though autosomal dominant and autosomal recessive patterns have been described. In an analysis of more than 470 CSNB cases, 57.9% of cases were X-linked, autosomal recessive and sporadic CSNB accounted for 40%, and the remaining 2.1% of cases were autosomal dominantly inherited [2]. To date, at least 21 genes have been reported to be implicated in CSNB, including *GRM6* [1,2,5–7]. *GRM6* mutations are responsible for autosomal recessive cCSNB, and the phenotype associated with *GRM6* mutation is variable in terms of presentation, refractive error, visual acuity and macular function, suggesting the genotype-phenotype correlation is not clear [8]. Genetic variants with potential functional sequences in *GRM6* were associated with high myopia [9,10], suggesting that *GRM6* may play a role in the development of myopia.

GRM6, localized on chromosome 5q35.3, contains 10 exons and encodes an 877 amino acid protein, metabotropic glutamate receptor 6 (mGluR6). mGluR6 contains two extracellular ligand glutamate-binding domains connected by a cysteine-rich region to the seven G protein-coupled receptor transmembrane domains with an intracellular C terminus. mGluR6 localizes in the dendritic tips of bipolar cells and is crucial for the glutamate uptake at the synaptic cleft [11,12]. In darkness, glutamate released from photoreceptors binds to mGluR6, and activates an intracellular cascade that terminates in closure of TRPM1 and hyperpolarization of the ON bipolar cells [6,13]. *GRM6* mutations cause absence of mGluR6 at the cell surface, interfere signal transmission from photoreceptors to ON bipolar cells and make the ON bipolar cells relatively depolarized (light adapted) in darkness, causing the symptom of night blindness and leading to a complete CSNB phenotype [6].

In this study, we aimed to explore the genetic defects of a family with autosomal recessive cCSNB from China.

2. Methods

2.1. Clinical evaluation of the participants

A Chinese family was recruited in the present study. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in compliance with regulations of the Declaration of Helsinki of the World Medical Association, and the protocol was approved by the Ethics Committee of Tianjin Medical University Eye Hospital (2021-KY03). The peripheral blood samples of the participants were obtained and drawn into an ethylenediamine tetraacetic acid (EDTA) sample tube for further analysis.

The patient accepted detailed ocular examinations, including visual acuity, intraocular pressure, anterior and posterior segment evaluation. Visual field examination was performed by Humphrey perimeter (Zeiss, Germany), fundus photos were obtained by Daytona Fundus Camera (Optos, England), and ERG was performed by RETI-Port (Roland, Germany).

2.2. DNA sequencing and data analysis

The method of targeted gene sequencing and data analysis was described elsewhere [14–16]. Briefly, we firstly extracted the genomic DNA from the blood samples according to the manufacturer's standard procedure (MagPure Buffy Coat DNA Midi KF Kit, Magen, China) and then sequenced the qualified genomic DNA with PE100 + 100 on MGISEQ-2000. We applied the NimbleGen SeqCap EZ Choice XL Library 24 Reaction 150217_HG19_CllnE_EZ_HX1 chip (Roche, Madison, USA) to capture the targeted sequences. The chip contains exons and their adjacent ±20 bp introns of 156 retinal diseases-related genes, which were described in detail previously [14]. The exonic deletions and duplications were also detected. Then, we performed bioinformatics processing and data analysis to detect the potential variants in the family after we received the primary sequencing data. All SNVs and indels were filtered and estimated via multiple databases, including NCBI dbSNP, HapMap, 1000 human genome dataset and database of 100 Chinese healthy adults. Finally, Sanger sequencing was used to validate all mutations and potential pathogenic variants. The Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php, retrieved on October 20, 2022) was used to screen mutations reported in published studies. The mutations were also blasted in ESP6500, ExAC, GnomAD, GnomAD-EAS, NCBI dbSNP, HapMap, 1000 human genome dataset and database of 100 Chinese healthy adults in order to rule out the possibility of a polymorphism.

2.3. Bioinformatics analysis of the mutations

We used online programs to predict the possible functional impact of the mutations, including BayesDel addAF, MetaLR, MetaRNN, MetaSVM, DEOGEN2, FATHMM, FATHMM-MKL, FATHMM-XF, LIST-S2, M-CAP, MutationTaster, PriamateAI, PROVEAN, SIFT, SIFT4G, and BayesDel noAF, etc by VarSome (http://varsome.com, retrieved on October 5, 2022). VarSome is a powerful annotation tool and search engine for human genomic variants, and can provide variants pathogenicity prediction scores from 20 different algorithms [17]. We also classified the variants into pathogenic or likely pathogenic variants, variants of uncertain significance, and benign or likely benign variants according to the standards described by the American College of Medical Genetics and Genomics (ACMG), in which each pathogenic criterion is weighted as very strong (PVS1), strong (PS1–4); moderate (PM1–6), or supporting (PP1–5) and each benign criterion is weighted as stand-alone (BA1), strong (BS1–4) or supporting (BP1–6) [18]. In addition, evolutionary conservation analysis was performed using Clustal Omega (an online package for making multiple sequence alignments of amino acid or nucleotide sequences [19], https://www.ebi.ac.uk/Tools/msa/clustalo/, retrieved on October 11, 2022) to identify a conserved region across species.

3. Results

3.1. Clinical evaluation of the participants

The proband, a 22-year-old girl, suffered from night blindness for more than 10 years (Fig. 1A). On presentation, the best corrected visual acuity was 20/20 (−5.5 DS+0.5 DC*40) and 20/25 (−6.0 DS+0.75 DC*60), the intraocular pressure was 15.1 mmHg and 16.7 mmHg, in the right eye and left eye, respectively. Under slit-lamp microscopy, the cornea was clear, the anterior chamber was deep and

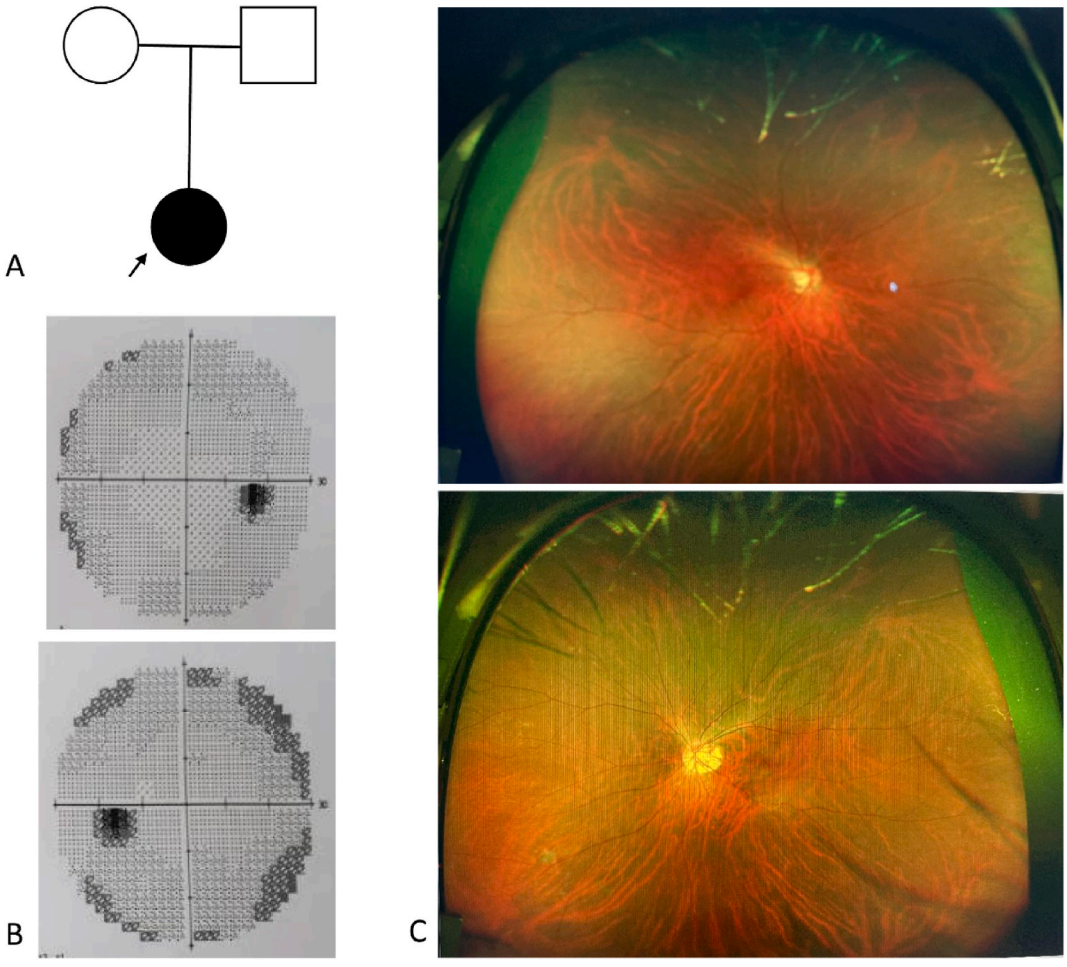

Fig. 1. Clinical evaluation of the patient. A: Pedigree map of the family, the arrow indicates the proband. B: Humphrey visual field examination showed no obvious visual field defects in both eyes. C: Fundoscopic examination revealed no abnormalities except myopic choroidal atrophy in both eyes.

quiet, the pupil was reactive to light and the lens was clear. Fundoscopic examination revealed no abnormalities except myopic choroidal atrophy in both eyes (Fig. 1C). Her color vision was normal and there was no nystagmus. Visual field examination (Humphrey SITA-Fast, central 30-2 threshold test) showed no obvious visual field defects (Fig. 1B). Scotopic 0.01 ERG showed no evident waves, scotopic 3.0 ERG showed a normal a-wave and a markedly decreased b-wave, scotopic 3.0 oscillatory potential ERG showed markedly decreased oscillatrory potentials both in numbers and amplitudes, and photopic 3.0 ERG and photopic 3.0 flicker 30Hz ERG showed normal waves in both eyes (Fig. 2). Based on the fundus appearance and the ERG changes, the patient was diagnosed complete Schubert-Bornschein type CSNB. The patient had no other ocular or systemic abnormalities. The parents of the proband were normal. There was no consanguineous marriage in this family.

3.2. Identification of mutations

Targeted gene sequencing containing 156 genes associated with retinal diseases was performed for the proband. The average read depth was 220.5X, the sequence coverage of the targeted region was 100% and the percentage of the average read depth over 15X was 99.86%. After filtering, two heterozygous mutations in *GRM6* were identified: c.152G>T (p.Gly51Val) and c.727delG (p.Val243SerfsX21). The mutations were further confirmed by Sanger sequencing (Fig. 3). Segregation analysis demonstrated that the mother of the proband carried the missense mutation (c.152G>T) while her father carried the frameshift mutation (c.727delG), indicating CSNB was autosomal recessively inherited in this family.

The carrier frequency of the frameshift mutation (c.727delG, p.Val243SerfsX21) found in this study was reported to be 0.000231938 in East Asians and 0.0000358 in Europeans [20], however, the detailed phenotype of the patients with this mutation is not available. Two other changes have been reported on codon 243. Heterozygous mutation c.727G>T, p.Val243Phe was found in a patient with CSNB, but the phenotype of the patient is not available [6]. One nucleotide insertion (c.720_721insG) was also reported in a patient with CSNB, which led to a frame shift at codon 243 and a premature stop codon 39 amino acids later [7]. The missense mutation (c.152G>T, p.Gly51Val) found in this study was previously described in a family with pseudodominant inheritance of autosomal recessive CSNB [21]. The proband, who carried the mutations p.Gly51Val and p.Arg621* in *GRM6*, had mild myopia, nystagmus and strabismus, which is different from the phenotype of the proband in our study, indicating the phenotypic variability of this disease even in patients carrying the same mutation.

The reported phenotype of the patients with *GRM6* mutations at codons 51 and 243 was summarized in Table 1. All the patients presented with night blindness, while the age at onset, visual acuity and refractive status varied among the patients.

We also found two heterozygous variants (c.3568G>A, p.Ala1190Thr and c.10859T>C, p.Ile3620Thr) in *USH2A* in the proband. Segregation analysis demonstrated that the mother of the proband carried the variant c.3568G>A, p.Ala1190Thr while her father carried the variant c.10859T>C, p.Ile3620Thr (Fig. 4). Although compound heterozygous mutations of c.10859T>C and c.9676C>T [22], c.10859T>G and c.7569G>A [23], c.10859T>C and c.12880delA [24] have been reported to be responsible for autosomal recessively inherited retinitis pigmentosa, the novel variant found in this study, c.3568G>A was predicted to be 'tolerated' by several online programs (http://varsome.com, retrieved on October 5, 2022) and its ACMG classification was 'Likely benign' (BP4+BP1+PM2, http://varsome.com, retrieved on October 5, 2022). Moreover, *USH2A* is implicated in Usher syndrome or retinitis pigmentosa [25], which is inconsistent with the phenotype of the patient. Taken above together, the heterozygous variants in *USH2A* found in this study are not considered to be disease-causing at present. However, Usher syndrome or retinitis pigmentosa can also be late-onset [26], and the patient was instructed to regular follow-up. No other variants were found in any other genes related to retinal disease.

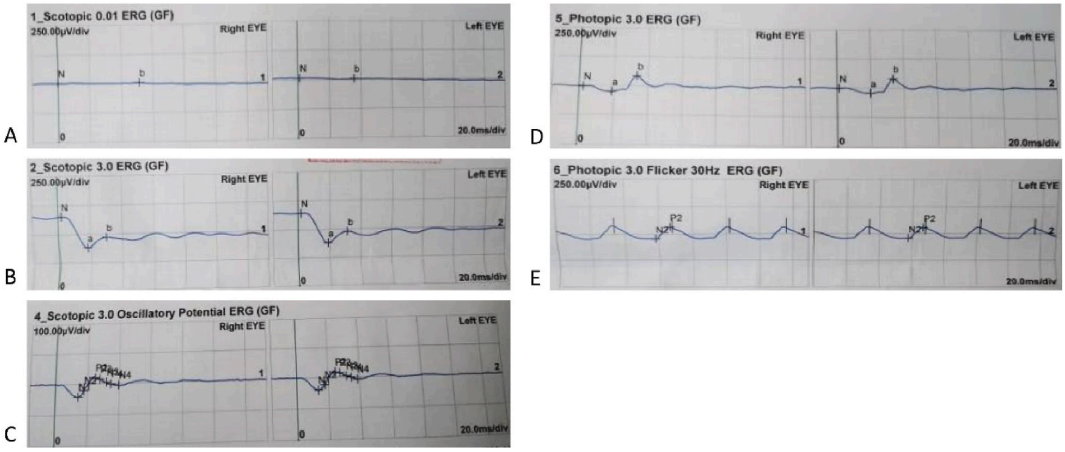

Fig. 2. Electroretinogram (ERG) result of the patient. A: Scotopic 0.01 ERG showed no evident waves. B: Scotopic 3.0 ERG showed a normal a-wave and a markedly decreased b-wave. C: Scotopic 3.0 oscillatory potential ERG showed markedly decreased oscillatrory potentials both in numbers and amplitudes. D: Photopic 3.0 ERG showed normal waves in both eyes. E: Photopic 3.0 flicker 30Hz ERG showed normal waves in both eyes.

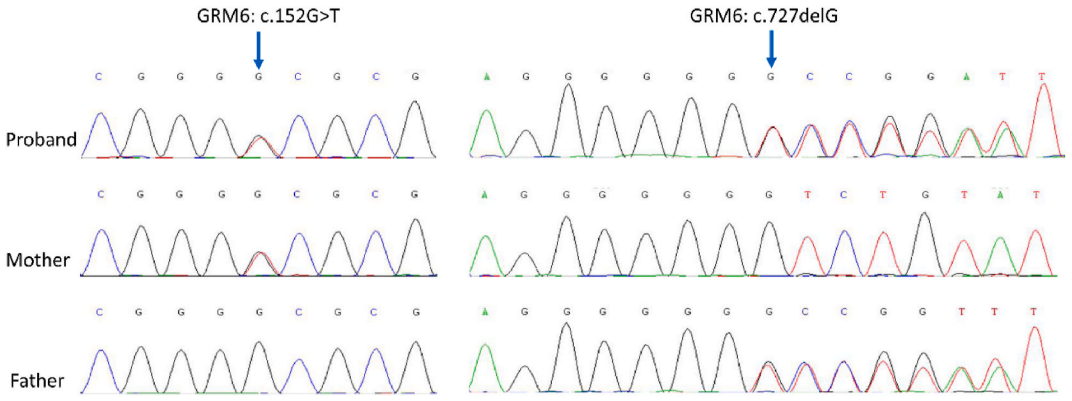

Fig. 3. Sanger sequencing of the *GRM6* mutations. The patient carried compound heterozygous mutations: c.152G>T (p.Gly51Val) and c.727delG (p.Val243SerfsX21). The mother of the proband carried the missense mutation (c.152G>T) while her father carried the frameshift mutation (c.727delG).

Table 1
Phenotype of the patients with GRM6 mutations at codons 51 and 243.

GRM6 mutations	Gender	Age (years)	Visual acuity (R; L)	Refractive error (R; L)	Night blindness	Nystagmus	Strabismus	Reference
c.152G>T and c.727delG	F	22	1.0; 1.0	−5.5D; -6D	Yes	No	No	Our study
c.727G>T	NA	NA	NA	NA	Yes	NA	NA	Dryja et al., 2005
c.720_721insG and c.137C>T	M	46	0.3; 0.1	+3.5D; +1.5D	Yes	Yes	NA	Zeitz et al., 2005
c.152G>T and c.1861C>T	M	NA	1.0; 1.0	−1.0 to −2.0D	Yes	Yes	Yes	Liu et al., 2019

NA: not available; F: female; M: male; R: right eye; L: left eye.

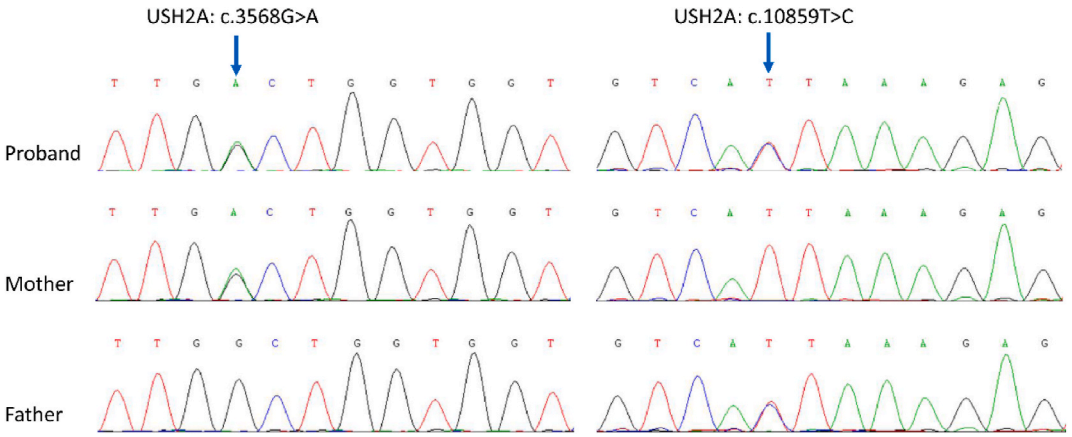

Fig. 4. Sanger sequencing of the *USH2A* variants. The patient carried two heterozygous variants (c.3568G>A, p.Ala1190Thr and c.10859T>C, p.Ile3620Thr) in *USH2A*. The mother of the proband carried the variant c.3568G>A, p.Ala1190Thr while her father carried the variant c.10859T>C, p.Ile3620Thr.

3.3. Bioinformatics analysis of the mutations

In order to predict whether the variants were deleterious, bioinformatics prediction programs were used to assess the functional effects of the mutation. Regarding the missense mutation (c.152G>T), BayesDel addAF, MetaLR, MetaRNN, MetaSVM, DEOGEN2, FATHMM, FATHMM-MKL, FATHMM-XF, LIST-S2, M-CAP, PriamateAI, PROVEAN, SIFT, and SIFT4G got a result of "Damaging"; MutationTaster got a result of "Disease Causing", BayesDel noAF showed a result of "tolerated", and REVEL got a result of 'Uncertain'. MutationTaster for the frameshift mutation (c.727delG) got a result of 'Disease Causing'. According to ACMG guidelines and standards, the missense mutation (c.152G>T) was defined as uncertain significance (PM2) and the frameshift mutation (c.727delG) was defined

as a pathogenic variant (PVS1+PP5+PM2). Evolutionary conservation analysis showed both Gly51 and Val243 were highly conserved among several species (Fig. 5). Together, these observations suggest that these changes are pathogenic variants.

4. Discussion

In this study, we detected compound heterozygous mutations (c.152G>T, p.Gly51Val and c.727delG, p.Val243SerfsX21) in *GRM6*, which are considered to be disease-causing for complete Schubert-Bornschein type CSNB.

To date, according to HGMD, more than 40 mutations in *GRM6* have been reported to be associated with CSNB, the majority of which are missense and nonsense mutations (Fig. 6). However, the exact phenotype-genotype correlation is still unclear [8]. The phenotypic variation might be resulted from the differences in disease penetrance, lifestyle, and environmental effects in different individuals [27]. Our findings broadened the phenotype and genotype spectrum of CSNB, and can help to elucidate the phenotype-genotype correlation in the future.

In our study, we detected a missense mutation (c.152G>T, p.Gly51Val) and a frameshift mutation (c.727delG, p.Val243SerfsX21) in *GRM6*, which were predicted to be disease-causing for complete Schubert-Bornschein type CSNB. The nonsense and frame-shift mutations in *GRM6* cause a loss of function of the receptor due to nonsense-mediated mRNA decay or non-functional receptor [2], while missense mutations lead to a trafficking defect of mGluR6 to the membrane [28], both of which will result in lack of the glutamate receptor at the cell surface. Consequently, the glutamate released from the cones and rods cannot be bind correctly to mGluR6 at the ON bipolar cell surface, resulting in defective signal transmission and leading to complete CSNB. This pathogenic mechanism was also proved in mouse models. Absence of protein or mislocalization of mutant mGluR6 was demonstrated for different mouse models mimicking *GRM6* gene defect [29–33]. The complete knockout mice lacking mGluR6 expression showed a loss of ON responses and unchanged OFF responses to light without obvious changes in retinal cell organization and projection of optic fibers to the brain, indicating mGluR6 is essential in synaptic transmission to the ON bipolar cells [29]. The *Grm6*^{nob4} model, generated by *N*-ethyl-*N*-nitrosourea mutagenesis, harbors a missense mutation in exon 3 (c.553T>C, p.Ser185Pro). In *Grm6*^{nob4} mice, the retinal structure was intact, but no immunoreactivity for mGluR6 was found and fewer retinal ganglion cells (RGC) responded to the onset of a bright full field stimulus [31]. The naturally occurring *Grm6*^{nob3} mouse carries a mutation in intron 2, which will lead to a novel splice site with a larger transcript and eventually cause a frame-shift mutation that would truncate the protein and produce a null allele. *Grm6*^{nob3} is allelic to *Grm6*^{nob4}, but when *Grm6*^{nob3} OFF-center RGC responses were evoked by full-field stimulation, significantly fewer converted that response to OFF/ON compared to *Grm6*^{nob4} RGCs [30]. The *Grm6*^{nob7} mouse carried a G to A transition at the last position in exon 8, which will disrupt splicing and crate a frameshift mutation truncating the normal protein by 170 amino acids and result in a null allele. In the *Grm6*^{nob7} retina, there is a loss of mGluR6 from the dendritic tips of depolarizing bipolar cells (DBC) [32]. Carrying the missense mutation p.Met66Leu, the *Grm6*^{nob8} mouse shows a reduced but not absent ERG b-wave, decreased but present expression of mGluR6 at DBC dendritic tips, and mislocalization of mGluR6 to DBC somas [33], which is different from the phenotype of other models. Conclusively, the phenotype of all these mouse models is similar to that of human patients with CSNB, and these models provide a useful tool to elucidate the role of mGluR6 in DBC signal transduction and can help us better understand the etiology

Fig. 5. Conservation analysis of *GRM6*. Both codons Gly51 and Val243 were highly conserved among several species. An asterisk sign (*) indicates a fully conserved residue, a colon sign (:) indicates conservation between groups of strongly similar properties, and a period sign (.) indicates conservation between groups of weakly similar properties.

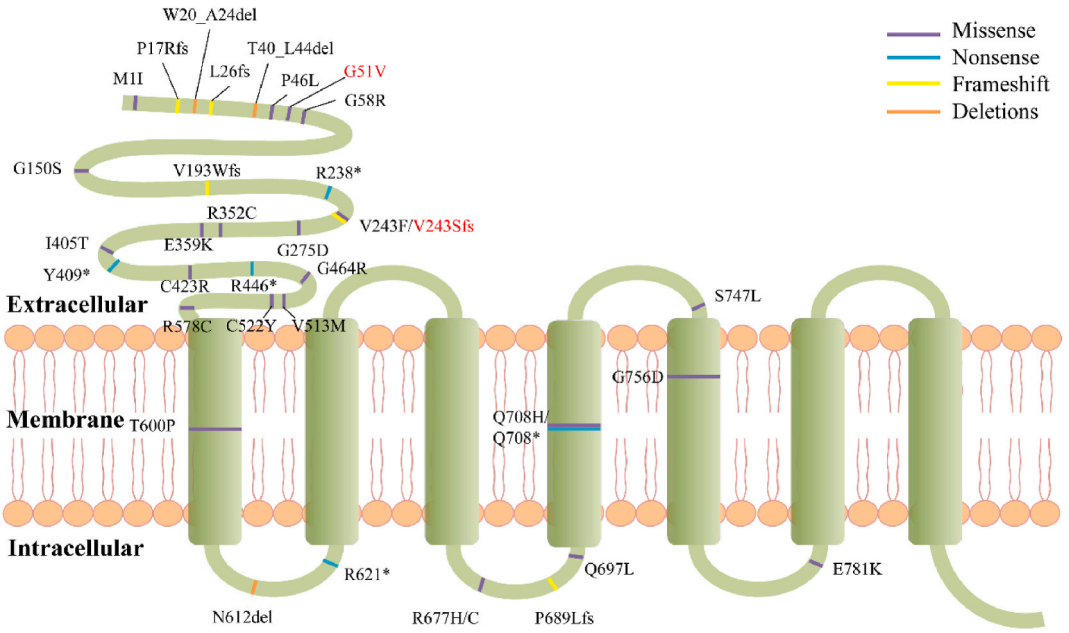

Fig. 6. Schematic structure of the mGluR6 protein and the reported *GRM6* mutations. The mutations found in this study were highlighted in red font. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and pathophysiology of CSNB.

To date, no treatment is available for CSNB. The Night Vision Spectacles were reported to improve the performance on the visual acuity, contrast sensitivity and motion contrast tests of patients with impaired night vision, especially at the low and high scotopic levels [34]. A combination therapy by drugs acting on the G_i, G_s, and G_q protein-couple receptors was demonstrated to protect the retina of diverse mice models of night blindness from light damage, providing a potential disease-modifying treatment strategy for retinal degenerative diseases [35]. Since CSNB is a stationary retinal disorder and the genetic background of this disease is well characterized, gene therapy has been proposed as a suitable approach to treat CSNB recently. Several studies evaluated the effect of adeno-associated virus (AAV)-based gene therapies targeting ON bipolar cells in animal models of cCSNB. In the *Nyx*^{nob} mouse model of cCSNB, intravitreal delivery of an AAV vector resulted in partial restoration of the ERG b-wave [36]. AAV2-7m8-*Lrit3* intravitreal injection was reported to achieve a recovery of ERG b-wave under scotopic conditions, improvement of optomotor responses, and functional rescue of on-time ON-responses at the ganglion cell levels, which were maintained for at least 4 months in adult *Lrit3*$^{-/-}$ mice [37]. By sub-retinal injection of the vector, AAV$^{K9\#4}$-*sh*GRM6-c*LRIT3*-WPRE, Miyadera et al. found significant recovery of rod-derived b-wave in all treated eyes (six of six) of adult dog models of CSNB [38]. The robust therapeutic effect was evident 7 weeks after injection and sustained for at least 1 year in all treated eyes. The only study of gene therapy aiming to rescue the phenotype due to the *GRM6* gene defect was performed by Varin et al. [39]. In their study, AAV-encoding *Grm6* under two different promoters (GRM6-*Grm6* and CAG-*Grm6*) were injected intravitreally in P15 *Grm6*$^{-/-}$ mice. Although no functional rescue was detected in ERG, the authors demonstrated restoration of mGluR6 localization at the dendritic tips of ON bipolar cells and relocalization of other partners of the cascade (TRPM1, GPR179, RGS7, RGS11, and Gβ5) after treatment. In this study, we found compound heterozygous mutations, c.152G>T, p.Gly51Val and c.727delG, p.Val243SerfsX21, were responsible for Schubert-Bornschein type CSNB, which could lay foundations for further gene therapy trials and provide new perspectives for treatment of CSNB.

In conclusion, by targeted gene sequencing and Sanger sequencing, we detected compound heterozygous mutations (c.152G>T, p.Gly51Val and c.727delG, p.Val243SerfsX21) in *GRM6* in a family with cCSNB. The mutations co-segregated with the phenotype of the family members and are considered to be responsible for complete Schubert-Bornschein type CSNB. However, functional experiments in the future are needed to confirm the pathogenicity of the variants and to elucidate their exact molecular mechanisms causing CSNB.

Ethics approval and consent to participate

This research followed the tenets of the Declaration of Helsinki of the World Medical Association, written informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. This study was approved by the ethics committee of Tianjin Medical University Eye Hospital.

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Dong'e Bai: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ruru Guo:** Data curation, Formal analysis, Funding acquisition, Writing – review & editing. **Dandan Huang:** Formal analysis, Writing – review & editing. **Jian Ji:** Conceptualization, Formal analysis, Supervision, Writing – review & editing. **Wei Liu:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We thank the family for their participation in this study.

List of abbreviations

CSNB	congenital stationary night blindness
RPE	retinal pigment epithelium
ERG	electroretinogram
cCSNB	complete congenital stationary night blindness
icCSNB	incomplete congenital stationary night blindness
mGluR6	metabotropic glutamate receptor 6
AAV	adeno-associated virus

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