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ORIGINAL ARTICLE

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Pseudodominant inheritance of autosomal recessive congenital stationary night blindness in one family with three co-segregating deleterious *GRM6* variants identified by next-generation sequencing

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Abstract

Background: The congenital stationary night blindness (CSNB) affects the patients' dim light vision or dark adaption by impairing the normal function of retina. It is a clinically and genetically heterogeneous disorder and can be inherited in an X-linked, autosomal dominant or autosomal recessive pattern. Several genetic alterations to the genes involved in visual signal transduction of photoreceptors and/or bipolar cells underlie its pathogenesis.

Methods: In this study, we used Sanger sequencing and next-generation sequencing (NGS)-based gene panel screening to investigate a family of three patients with CSNB inherited in an apparent autosomal dominant pattern. We expected to find out the disease-causing gene defects carried by this family.

Results: We found that the patients in this family did not carry the *RHO*, *GNAT1*, or *PDE6B* mutation, but carried compound heterozygotes mutations of *GRM6*. Three deleterious *GRM6* variants, p.Arg621Ter, p.Gly51Val, and p.Gly464Arg, were found to be co-segregating with the disease, causing a pseudodominant inheritance of *GRM6*-related autosomal recessive complete CSNB.

Conclusion: This study presents a rare case of autosomal recessive CSNB (arCSNB) pseudodominant inheritance, which potentially leads us to expand our gene candidate list in future genetic testing for apparent dominant pedigrees. The discovery of the two novel likely pathogenic variants p.Gly51Val and p.Gly464Arg could broaden our knowledge about the genetics of CSNB and provide insights into the structure and function of the GRM6 protein.

KEYWORDS

congenital stationary night blindness, *GRM6*, next-generation sequencing, pseudodominant inheritance

1 | INTRODUCTION

Congenital stationary night blindness (CSNB) is a group of nonprogressive retinal disorders with clinical and genetic heterogeneity (Zeitz, Robson, & Audo, 2015). Patients with this disease have impaired night vision or poor adaption to darkness. Poor visual acuity, myopia, photophobia, nystagmus, strabismus, and fundus abnormalities are other possible

manifestations associated with some forms of CSNB (Zeitz et al., 2015). To date, 17 genes have been implicated in the pathogenesis of this disease, most of which are crucial for the normal function of photoreceptor or bipolar cells (Zeitz et al., 2015).

CSNB with normal fundi is divided into Riggs, (1954) and Schubert-Bornschein (Schubert & Bornschein, 1952) subtypes according to electroretinography (ERG) patterns. The latter further diverges into two forms, the complete (cCSNB) and the incomplete (icCSNB)(Miyake, Yagasaki, Horiguchi, & Kawase, 1987; Miyake, Yagasaki, Horiguchi, Kawase, & Kanda, 1986). Riggs-type CSNB presents a reduced a-wave and reduced b-wave, while Schubert-Bornschein-type has a normal a-wave in addition to a severely reduced b-wave under scotopic conditions at a bright flash. In contrast to icCSNB, cCSNB has no detectable ERG to a dim flash. These CSNB subtypes possess its own specific inheritance patterns and distinct gene drivers. Today, autosomal dominant CSNB (adCSNB) is only associated with Riggs phenotype driven by *RHO* (OMIM: 180380; Dryja, Berson, Rao, & Oprian, 1993), *GNAT1* (OMIM: 139330; Dryja, Hahn, Reboul, & Arnaud, 1996), or *PDE6B* (OMIM: 180072; Gal, Orth, Baehr, Schwinger, & Rosenberg, 1994); X-linked CSNB (xlCSNB) is associated with *NYX* (OMIM: 300278; Bech-Hansen et al., 2000; Pusch et al., 2000) and *CACNA1F* (OMIM: 300110; Bech-Hansen et al., 1998; Strom et al., 1998); autosomal recessive CSNB (arCSNB) could be complete, incomplete or Riggs-type, which may be caused by *GRM6* (OMIM: 604096; Dryja et al., 2005; Zeitz et al., 2005), *TRPM1* (OMIM: 603576; Audo et al., 2009; Li et al., 2009; van Genderen et al., 2009), *GPR179* (OMIM: 614515; Audo et al., 2012; Peachey et al., 2012), *LRIT3* (OMIM: 615004; Zeitz et al., 2013), *CABP4* (OMIM: 608965; Zeitz et al., 2006), *CACNA2D4* (OMIM: 608171; Wycisk, Budde, et al., 2006; Wycisk, Zeitz, et al., 2006), *SLC24A1* (OMIM: 603617)(Riazuddin et al., 2010), or *GNAT1* (OMIM: 139330) (Naeem et al., 2012).

In this study, we used Sanger sequencing and NGS-based gene panel screening to investigate a family with three patients affected by CSNB inherited in an apparent autosomal dominant pattern. We aimed to identify potential gene defects underlying the case.

2 | METHODS AND MATERIALS

2.1 | Ethical compliance

Four members of the pedigree (II3, II4, III3, and III4 in Figure 1) and a control (Figure S1) were included in this study, which was carried out in accordance with the tenets of the Declaration of Helsinki and was approved by the Internal Review Board of Henan Provincial People's Hospital, People's Hospital of Zhengzhou University. Informed consent was obtained from the participants for the study.

2.2 | ERG examination

ERG was performed according to ISCEV standard for full-field clinical ERG (McCulloch et al., 2015). For scotopic condition, 0.01/3.0/10.0 cd.s.m^{-2} and oscillatory potentials ERG were performed. For photopic condition, 3.0 cd.s.m^{-2} and 30 Hz Flicker ERG were performed.

2.3 | Gene panel screening

The screening of the proband for genetic variants was performed with Illumina TruSight^{TM} One Sequencing Panel following the manufacturer's instructions. 150-bp paired-end reads were generated with an Illumina MiSeq platform. Sequencing data were analyzed with MiSeq Reporter (Illumina) and variant annotation was performed with VariantStudio (Illumina).

2.4 | In silico prediction

The function of genetic variants was predicted in silico with PolyPhen-2 (Adzhubei et al., 2010), PROVEAN (Choi, Sims, Murphy, Miller, & Chan, 2012), and MutationTaster (Schwarz, Cooper, Schuelke, & Seelow, 2014) following the instructions on their online interfaces and using default parameters.

2.5 | Database accessibility

Clinical significance of variants was obtained from ClinVar (Landrum et al., 2016) (May 13, 2019; https://www.ncbi.nlm.nih.gov/clinvar/). Allele frequency was obtained from ExAC (Lek et al., 2016) (release 1.0 updated February 27, 2017; http://exac.broadinstitute.org/) and gnomAD (Lek et al., 2016) (version 2.0.2 updated October 3, 2017; http://gnomad-old.broadinstitute.org/).

2.6 | Sanger sequencing of GRM6

The following primers were used to screen *GRM6*. GRM6-E2-3F: TGTTCAGGACACAGCTTGTACC. GRM6-E2-3R: CTATTCAGTCTGGGCTTGTGGC. GRM6-E4F: CCTCTGAACCCCCTGAACAG. GRM6-E4R: CAATTCCTCCCCGTCCAGTG. GRM6-E5-6F: GTTCACCTGGCCACTCCTAG. GRM6-E5-6R: TAGACCACTCAGCCTCACCC. GRM6-E7-8F: CGGCTTGGATTTGCACGTCC. GRM6-E7-8R: CCTTTTGGCTTTGTAACGTTGC. GRM6-E9F: AGAGCCTCAAGGGGATCCTG. GRM6-E9R: AACAAGCAGCCAGATACGGG. GRM6-E10F: GTGCTCATTCCCAGTTCCCC. GRM6-E10R: TGGTCTTGGCAAACTCCCTG.

2.7 | Reference sequences

The nomenclature of *GRM6* variants in this study is based on GenBank NM_000843.3.

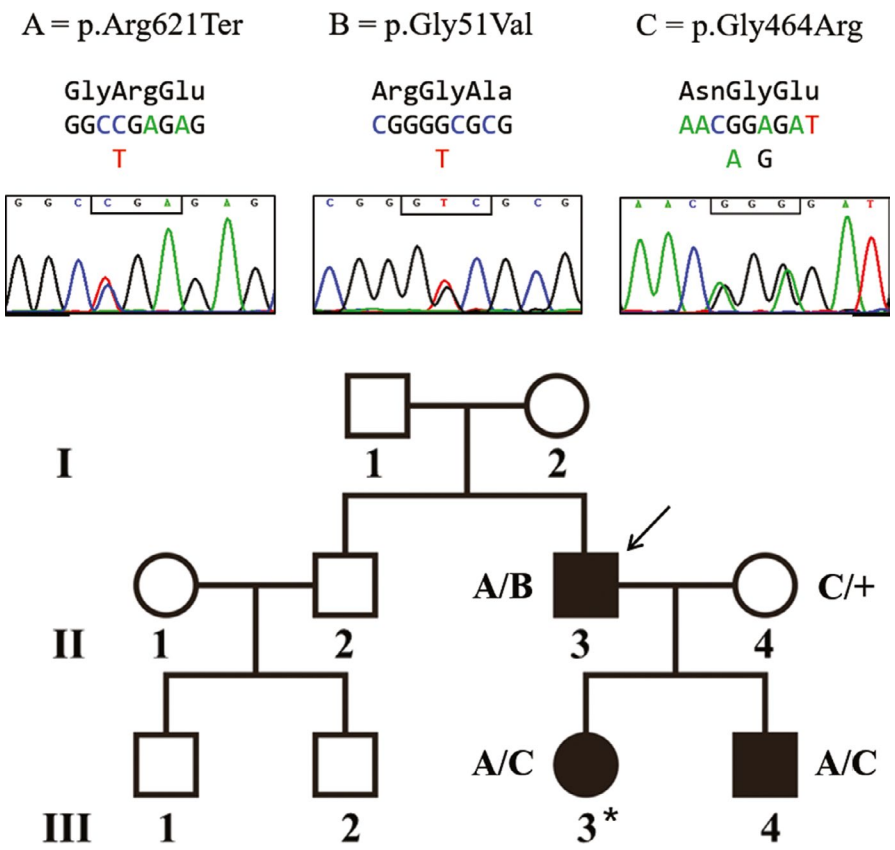

FIGURE 1 The pedigree and *GRM6* variants of the CSNB family. Top: *GRM6* variants carried by the family and corresponding Sanger sequencing results, p.Arg621Ter (c.1861C>T, CGA to TGA), p.Gly51Val (c.152G>T, GGC to GTC), and p.Gly464Arg (c.1390G>A, GGA to AGA). Another single nucleotide variant c.1392A>G can be also observed in the top right. It is at the wobble position of codon 464, synonymous and benign. (*GRM6*: NM_000843.3) Bottom: the CSNB family's pedigree with genotype. Arrow marks the proband and asterisk marks the clinically evaluated member

3 | RESULTS

As shown in Figure 1, three members in a pedigree were affected by CSNB, the proband (II3) and his two children (III3 and III4). All the three patients had mild myopia (−1.0 to −2.0 D) with mild astigmatism; the uncorrected visual acuity of them was between 0.3 and 0.5 whereas the corrected visual acuity could reach 1.0. The proband had nystagmus and strabismus. Both of his children had amblyopia. His partner (II4) had no symptoms of CSNB. The children were diagnosed with night blindness when 4–5 years old. The age of the proband at diagnosis was not available. When the pedigree was received by Genetic Counseling Clinic, Henan Provincial People's Hospital, no properly performed ERG was available.

The night blindness transmission from the proband to his son ruled out the possibility of X-linked inheritance (Figure 1). Initially, we assumed the disease was inherited autosomal dominantly. Three genes underlying adCSNB, *GNAT1*, *RHO*, and *PDE6B*, were screened on the proband with Sanger sequencing, but no variant was found.

Next, TruSight™ gene panel sequencing was performed on the proband. Two *GRM6* variants were identified and subsequently validated via Sanger sequencing (Figure 1). One is p.Arg621Ter (c.1861C>T, CGA to TGA) leading to a premature truncation of the protein, which had been reported to be pathogenic (Dryja et al., 2005); the other p.Gly51Val (c.152G>T, GGC to GTC) was a rare variant documented in gnomAD and predicted as a deleterious variant by PolyPhen-2, PROVEAN, and MutationTaster (Table 1). Therefore, the proband was identified as a compound heterozygote of p.Arg621Ter and p.Gly51Val and possibly affected by autosomal recessively inherited *GRM6*-related CSNB.

Sanger sequencing targeting *GRM6* was then carried out for the proband's children. It was found that the son and the daughter were both compound heterozygous for p.Arg621Ter and p.Gly464Arg (c.1390G>A, GGA to AGA) of *GRM6* (Figure 1). Since the proband did not carry p.Gly464Arg, his partner was Sanger-sequenced and then found to be a p.Gly464Arg carrier (Figure 1). p.Gly464Arg was a rare variant documented in both ExAC and gnomAD, and predicted to be deleterious (Table 1).

Together with the proband's genotype, in this family three deleterious *GRM6* variants, p.Arg621Ter, p.Gly51Val, and p.Gly464Arg, were identified, which could explain the apparent autosomal dominant inheritance pattern of *GRM6*-related arCSNB in the pedigree. By the criteria of ACMG (Richards et al., 2015), both of the missense variants were classified into Likely Pathogenic category.

In addition to p.Arg621Ter and p.Gly464Arg, the children were also found to be carriers of c.1392A>G (Figure 1, Top Right), which was a single nucleotide polymorphism (rs11746675) at the wobble position of codon 464, and

TABLE 1 The documented allele frequency and the predicted pathogenicity of p.Gly51Val, p.Gly464Arg, and p.Arg621Ter

Variant	p.Gly51Val	p.Gly464Arg	p.Arg621Ter
ClinVar			
Clinical significance	N.D.	N.D.	Pathogenic
ExAC			
Allele frequency	N.D.	1/115892	21/118580
gnomAD			
Allele frequency	1/27876	2/245570	44/276352
PolyPhen-2			
Prediction	Probably damaging	Probably damaging	N.P.
Score, HumDiv	0.999	1.000	N.P.
Score, HumVar	0.993	0.990	N.P.
PROVEAN			
Prediction	Deleterious	Deleterious	N.P.
Score	−6.120	−7.598	N.P.
MutationTaster			
Prediction	Disease causing	Disease causing	N.P.
Probability	1.000	1.000	N.P.

GRM6: NM_000843.3.
Abbreviations: ND, not documented; NP, not performed.

did not alter amino acid sequence of the protein or locate in a splice site. Its frequency in ExAC and gnomAD were 71592/119380 and 164878/275666, respectively. ClinVar documented it as a benign variant.

GRM6-related CSNB was the complete form of this disease. To subtype the CSNB of the pedigree, the daughter and a control were recruited to take ERG examination. From the result (Figure S1 and Table S1), we could see that the daughter showed a dark-adapted ERG of negative waveforms with a normal a-wave and a severely reduced b-wave, which matched the characteristic of cCSNB. The ERG results indicated that the function of bipolar cells and amacrine cells in both eyes of the daughter decreased, while other functions were basically normal.

4 | DISCUSSION

In this study, we reported a rare case of pseudodominantly inherited arCSNB in a family with three co-segregating deleterious variants of *GRM6*. To our knowledge, this is the first report of CSNB pseudodominant inheritance, and the first report of likely pathogenic variants p.Gly51Val and p.Gly464Arg in *GRM6*-related CSNB.

Pseudodominant inheritance of autosomal recessive diseases happens when a homozygote (or compound heterozygote) has a partner with a heterozygous mutation. Higher carrier frequency in a population brings higher incidence of this phenomenon. Similar cases also have been reported in *DUOX2*-caused nonautoimmune hypothyroidism and *GDAP1*-caused Charcot-Marie-Tooth type 2 (Abe, Narumi, Suwanai, Hamajima, & Hasegawa, 2015; van Paassen et al., 2017). Although adCSNB is usually caused by *RHO*, *GNAT1*, or *PDE6B* defects, this study reminds us that some apparent autosomal dominant CSNB can also be caused by some other autosomal recessive genes. Considering the possibility of this situation, unbiased methods like next-generation sequencing simultaneously targeting multiple genes are more helpful when patients' clinical manifestations are unclear.

GRM6 is a gene localized on chromosome 5q35.3. It encodes a 7-transmembrane protein of 877 amino acid residues, which belongs to human metabotropic glutamate receptor family and is specifically expressed in ON bipolar cells. GRM6 protein is important for the signal transmission at the postsynaptic site upon light stimulation. In 2005, two research groups reported that several *GRM6* variants, including p.Leu26fs, p.Pro46Leu, p.Gly58Arg, p.Gly150Ser, p.Val243fs, p.Cys522Tyr, p.Arg621Ter, p.Glu708Ter, and p.Glu781Lys, could lead to cCSNB in an autosomal recessive manner (Dryja et al., 2005; Zeitz et al., 2005). The variants discovered in this study are both located in the extracellular region of GRM6 spanning from Gly25 to Trp585. Multiple sequence alignment by Clustal Omega suggested Gly51 of GRM6 to be conserved in its family members GRM2 (Gly44), GRM3 (Gly51), GRM4 (Gly61), GRM7 (Gly61), and GRM8 (Gly58), whereas Gly464 is conserved in all eight members of the family (data not shown). This conservation indicates the functional importance of both residues.

The structure of human GRM6 has not been resolved. From determined structures of its family members, we could infer that Gly51 and Gly464 both reside in the unstructured regions out of flanking alpha helices and/or beta strands, and not involved in the direct contact with the ligand glutamate. In 2007, Zeitz et al. investigated the impact of missense variants in GRM6 and found CSNB-associated variants p.Pro46Leu, p.Gly58Arg, p.Gly150Ser, p.Ile405Thr, p.Cys522Tyr, and p.Glu781Lys all translocated V5-GRM6 from cell surface to endoplasmic reticulum in HEK293T cells (Zeitz et al., 2007). p.Gly51Val and p.Gly464Arg may apply similar mechanism to cause CSNB.

Findings in this report remind us to consider the possibility of pseudodominance when facing an apparent autosomal dominant pedigree of CSNB. This potentially leads us to expand gene candidate list in genetic testing. Besides, the discovery of p.Gly51Val and p.Gly464Arg adds to our knowledge of CSNB disease and broaden the genotypic spectrum of *GRM6*. Screening of these novel variants in

GRM6 since the early stage of diagnosis will benefit future patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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