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A *GUCY2D* variant associated cone-rod dystrophy with electronegative ERG: A case report and review

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ABSTRACT

Purpose: Cone-rod dystrophies (CORD) are inherited retinal dystrophies characterized by primary cone degeneration with secondary rod involvement. We report two patients from the same family with a dominant variant in the guanylate cyclase 2D (*GUCY2D*) gene with different phenotypes in the electroretinogram (ERG).

Observations: A 21-year-old lady (Patient 1) was referred due to experiencing blurry vision and color vision impairment. Visual field testing revealed a central scotoma. Spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) documented macula dysfunction. Reduced amplitude was observed in the photopic responses of ERG. Her 54-year-old father (Patient 2) had similar issues with blurry vision. A dilated fundus examination displayed bilateral macular atrophy. Loss of the ellipsoid zone line and collapse of the outer nuclear segment were noted on the SD-OCT. Photopic ERG responses were extinguished, and an electronegative ERG was observed in the dark-adapted 3.0 ERG. The gene report revealed a c.2512C > T (p.Arg838Cys) variant in *GUCY2D* for both patients. They were respectively diagnosed as cone dystrophy (COD) and cone-rod dystrophy (CORD).

Conclusions: We report two different clinical phenotypes in *GUCY2D*-associated COD despite sharing the same variant. A dysfunction in the synaptic junction between the photoreceptor and the secondary neuron was proposed to explain the electronegative ERG. This explanation might extend to other gene-related cases of CORD with electronegative ERG.

1. Introduction

Inherited retinal dystrophies (IRD) are a group of heterogeneous disorders caused by variants in genes that are important for retinal function.[1] Cone-rod dystrophy (CORD) is an IRD characterized by progressive central vision loss due to the degeneration of photoreceptors. In the early stages, the disease is marked by the dysfunction of cones followed subsequently by the involvement of rods over time. Although CORD is a clinically recognizable entity, collectively, it is genetically heterogeneous. To date, pathogenic variants in more than 32 genes are known to underlie CORD.[2] A major cause of CORD is attributable to variants in the *GUCY2D* (MIM *600179) gene which encodes the retinal-specific enzyme guanylate cyclase 2D.[3] Both autosomal dominant (AD) and autosomal recessive (AR) inheritance patterns have been reported in patients with *GUCY2D*-associated CORD.[4–6] *GUCY2D* variants account for the largest fraction of known AD cone-/cone-rod dystrophy (AD- COD/CORD) cases.[2,7] *GUCY2D* encodes the protein retinal guanylate cyclase, an enzyme expressed predominately in cone cells,[8]

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and functions in the recovery stage of phototransduction.[9]

Initial symptoms for AD COD-/CORD included reduced visual acuity (VA), photophobia, variable degrees of dyschromatopsia, and central scotomas in the visual field. Delays in implicit time and reductions in amplitude observed in both 30Hz flicker electroretinogram (ERG) and single-flash photopic ERG suggest a generalized dysfunction of cone cells. As the disease progresses, visual acuity continues to deteriorate while some patients start to experience night blindness and nystagmus.[10] Over time, scotopic ERG responses would also be affected, indicating the involvement of rod cells. Thus, ERG patterns have been employed as a diagnostic tool for identifying COD/CORD.

In this article, we report two patients, a daughter (Patient 1) and her father (Patient 2), respectively diagnosed with AD-COD and AD-CORD. Whole exome sequencing identified the heterozygous variant of c.2512C > T (p.Arg838Cys) in the *GUCY2D* gene in both cases. Patient 2 also showed an electronegative ERG pattern, which is infrequently seen in patients with AD-CORD. This report expands the clinical spectrum of and differential findings in *GUCY2D*-associated CORD.

2. Case presentation

2.1. Case 1

The proband is a 21-year-old woman who presented to our department with a history of persistently uncorrectable visual acuity since childhood, coupled with color vision impairment. There was no reported consanguinity in her family history (Fig. 1).

At initial examination, her VA was correctable to 20/40 in the right eye and 20/60 in the left eye. Ophthalmic history included myopia with 6 diopters. Intraocular pressure was within the normal range, measuring 17 mmHg in both eyes. Upon reviewing her fundus photos, a slight enlargement in the cup-to-disc ratio was observed (Fig. 2). Therefore, she was initially diagnosed with normal tension glaucoma (NTG). However, her visual field analysis did not match that of a typical NTG patient, as both eyes displayed a central scotoma (Fig. 2). Fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT) were performed on the patient. The FAF revealed symmetric dark lesions with well-demarcated increased autofluorescence borders in the central macula of both eyes. The corresponding area with the lesion on OCT was characterized by the thinning of the outer nuclear layer in the fovea, while the ellipsoid zone (EZ) line was partially preserved in the fovea in both eyes. The retinal nerve fiber layer appeared normal in both eyes (Fig. 2). These findings prompted us to reevaluate the original diagnosis. Full-field electroretinography (ff-ERG) showed normal scotopic responses in both eyes. However, the amplitudes were attenuated and implicit times were delayed in both light-adapted 3.0 ERGs and 30 Hz flicker ERGs (Fig. 4). These results indicate extensive cone system dysfunction, rather than NTG. Therefore, we suspected her of having cone dystrophy. Dark-adapted 10.0 ERG was not recorded, as the ERG work-up was performed before the International Society for Clinical Electrophysiology of Vision.[11] (ISCEV standard protocol for ff-ERG in 2015 year)

2.2. Case 2

The second patient, the father of patient 1, was a 54-year-old man who had experienced blurry central vision for the past 10+ years. His ophthalmologic history also included myopia with 3 diopters and color vision defects. He has no family history of similar ocular diseases, except for his daughter (Case 1) (Fig. 1).

Upon presentation, BCVA was 20/200 in both eyes. Intraocular pressures were 17 mmHg in the right eye and 16 mmHg in the left eye. Fundus examination showed macular atrophy and lesions in both eyes (Fig. 3). FAF imaging demonstrated an outer ring with increased autofluorescence and a decreased autofluorescence region within the ring in the macula. His OCT results indicated a loss of the EZ line in the fovea of both eyes, with the outer nuclear layer line preserved but collapsed in the central macula (Fig. 3). These findings pointed to damage in the macula cone photoreceptor cells. The scotopic dark-adapted 0.01 ERG response showed a delayed implicit time in both eyes. Additionally, the dark-adapted 3.0 ERG displayed a reduction in the b-wave amplitude, recording an electronegative ERG pattern. Photopic ERG responses and 30Hz flicker ERGs were non-recordable, indicating a total loss of cone function in both eyes (Fig. 4). These observations were consistent with a comprehensive loss of cone cell function and damage to rod cell function, typical of CORD.

2.3. Genetic results

Since COD-/CORD-are hereditary conditions and considering the apparent vertical transmission of the disease between the two patients, we performed whole exome sequencing in both individuals. (The test was done by 3 billion company: 13F, 416, Teheran-ro, Gangnam-gu, Seoul, Republic of Korea (06193), a CLIA-certified lab.) This analysis revealed a heterozygous missense variant c.2512C > T (p.Arg838Cys), in the *GUCY2D* gene for both patients. Based on the identification of the same heterozygous variant in both the daughter and father, we have concluded that the CORD follows an autosomal dominant inheritance pattern. This observation is consistent with prior studies on CORD associated with mutations in the *GUCY2D* gene, suggesting an

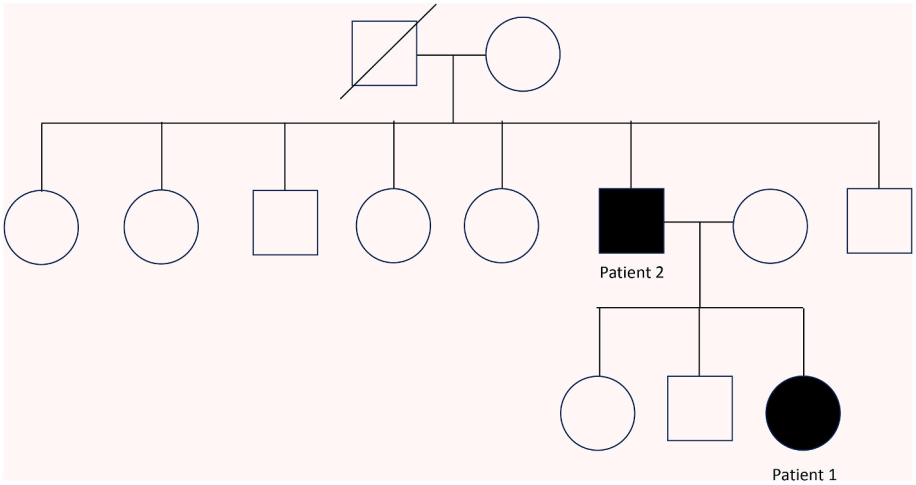

Fig. 1. Family pedigree of both patients. Two patients are in a father-daughter relationship. No family history of cone-rod dystrophy. (CORD).

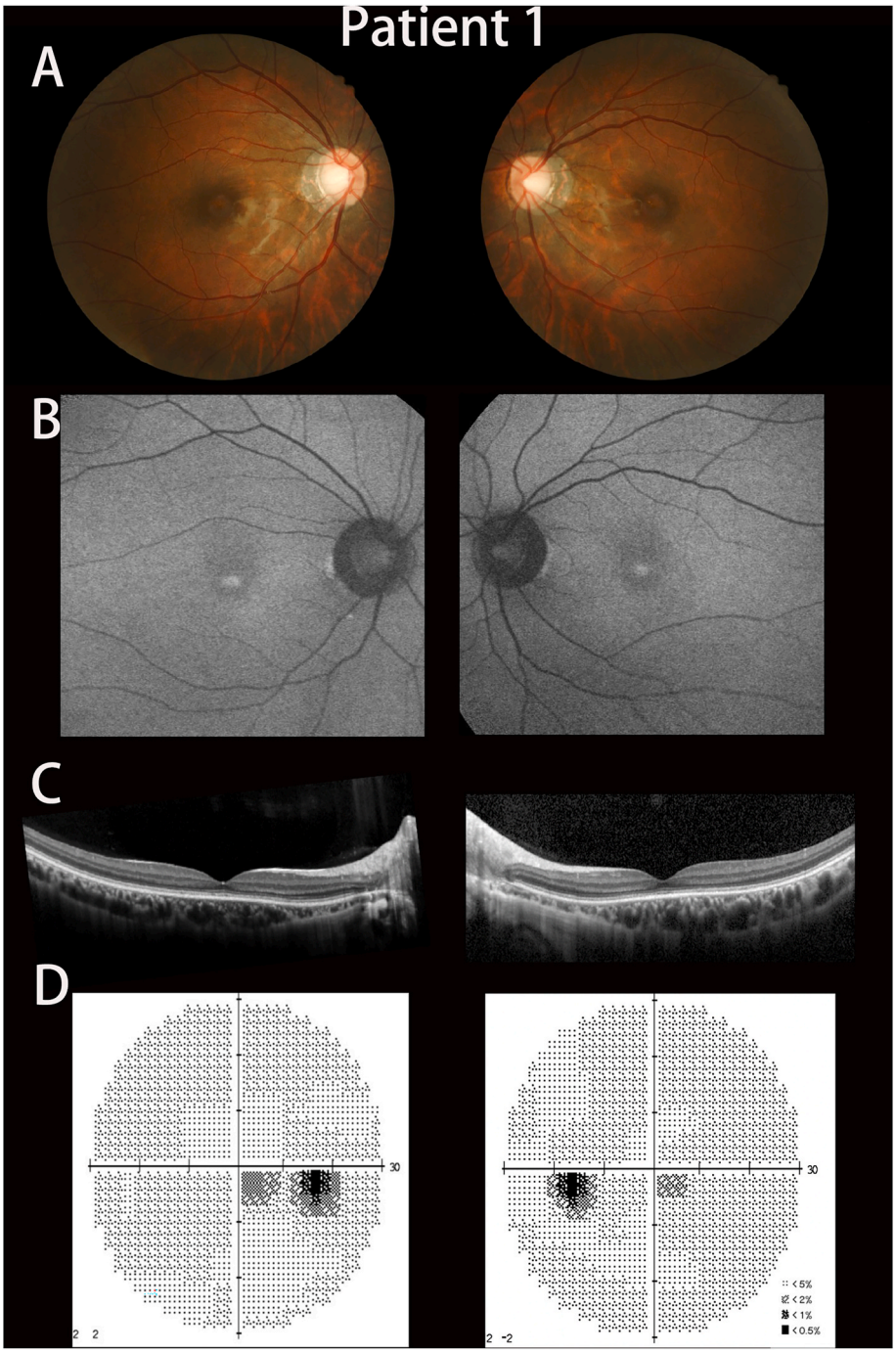

Fig. 2. Color fundus, fundus autofluorescence, (FAF) optical coherence tomography (OCT) imaging, and visual field test for patient 1. A. Fundus image revealed slight enlargement of the optic disc in both eyes. B. FAF revealed a hypoautofluorescence area in the macula in both eyes. C. OCT revealed a loss of the outer nuclear layer in the central macula in both eyes. D. Visual field test results. A central scotoma was present in both eyes of patient 1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

autosomal dominant inheritance pattern. The identified variant is deemed likely pathogenic based on *in silico* predictions (CADD-PHRED = 29.5, Eigen = 0.8447, M-CAP = 0.6338) and multiple independent reports of this variant in cases with a similar disease phenotype.[12–15] No other relevant variants in retinal disease-associated genes shared between both patients were identified. These results provided molecular confirmation of our clinical diagnosis of AD-COD for patient 1 and AD-CORD for patient 2.

Both variants were confirmed by using pair-end Sanger sequencing. The pathogenicity of each variant on its associated diseases was evaluated according to the recommendations of the standard and guideline of the American College of Medical Genetics and Genomics (ACMG) guideline.[16]

3. Discussion

Our case report describes two patients, a lady, and her father, diagnosed with AD-COD and AD-CORD, respectively, due to a heterozygous missense variant c.2512C > T (p.Arg838Cys) in the *GUCY2D* gene. Patient 2 showed an electronegative ERG pattern, which is more

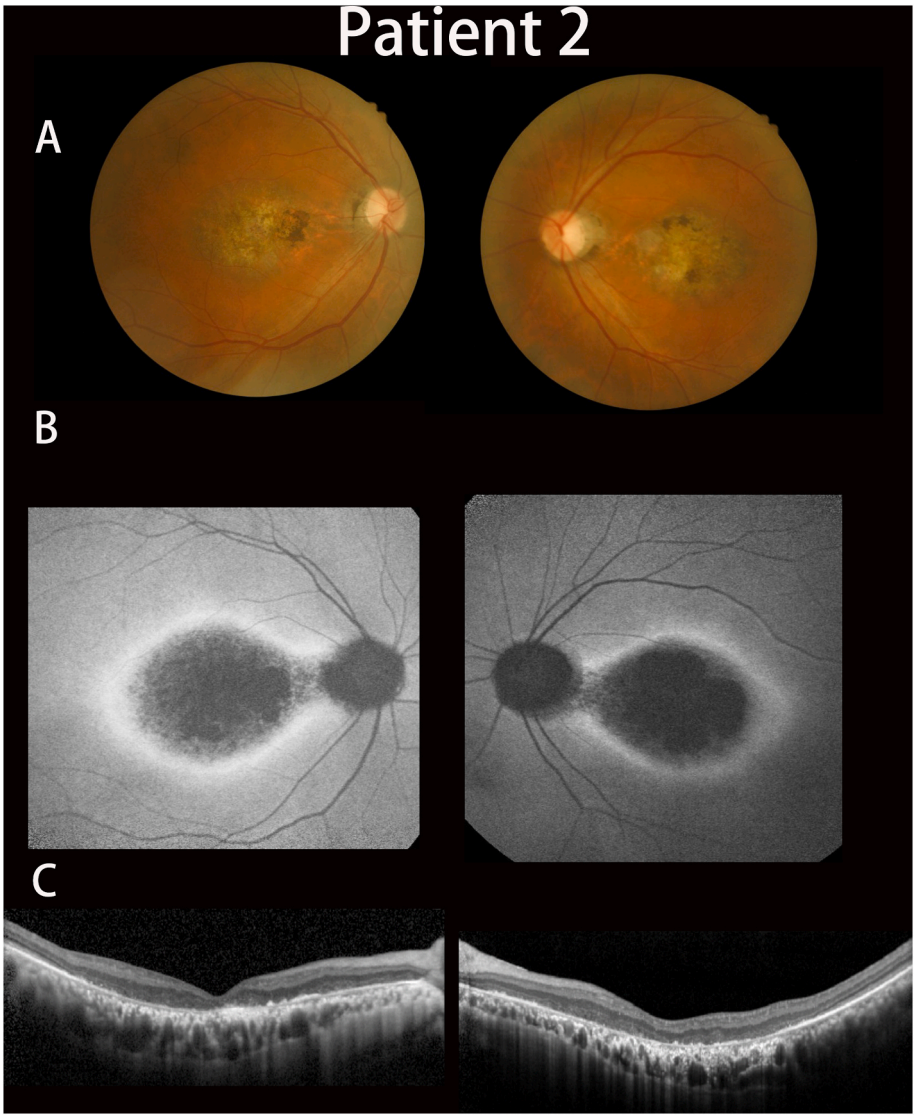

Fig. 3. Color fundus, fundus autofluorescence, (FAF) optical coherence tomography (OCT) imaging, and visual field test for patient 2. A. Fundus image for patient 2 revealed atrophic lesions in both eyes. B. FAF imaging for patient 2 revealed an outer ring exhibiting increased autofluorescence, with decreased autofluorescence observed within the ring in both eyes. C. OCT of patient 2 revealed a loss of the ellipsoid zone (EZ) line and a collapse of the outer nuclear layer in the central macula in both eyes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

commonly seen in other *GUCY2D*-associated diseases such as congenital stationary night blindness (CSNB; MIM #618555)[17–19] and X-linked retinoschisis.

The association of the *GUCY2D* variant with AD COD/CORD was first reported by Kelsell et al., who identified two missense variants, p. Glu837Asp and p.Arg838Cys as pathogenic.[4] Subsequent studies have also identified *GUCY2D* variants at the same locus (c.2512C > T, p. Arg838Cys) as a significant factor associated with an increased risk of AD COD/CORD. The association is observed among both unrelated patients[12,15,20] and co-segregate among affected relatives in both the same family and unrelated families with similar phenotypes.[7,12,15,21] The functional assays revealed that the variant p.Arg838Cys exhibited a moderate level of impact, leading to inactivation under high Ca^{2+} concentration.[22] According to ClinVar, both the c.2512C > T, p.Arg838Cys variants and different missense changes at the same codon have been reported variants as pathogenic or likely pathogenic with strong evidence.[7,13] (ClinVar Variant ID: VCV000009357.44, VCV000811743.40) Multiple in-silico tool predictions suggest the variant gene product as pathogenic moderate. (REVEL: 0.799; 3CNET: 0.827; CADD: 27.9) The mutant was also reported at a very low frequency according to the gnomAD v4.0 dataset. (Total genome frequency: 0.00000658; total exome frequency: 0.0000041; total allele frequency: 0.000004338) Hence, the variant reported should be classified as pathogenic according to the ACMG guideline.[16]

The present report documents a case of a CORD patient exhibiting an electronegative ERG, a finding that has been infrequently reported in previous cases of patients with *GUCY2D* variants associated with COD/CORD. Also, we report different clinical phenotypes among patients with the same gene variant. Despite sharing the same familial origin and carrying identical variants, our two patients showed discordant clinical phenotypes, especially evident in their rod cell functionality.

A contributing factor to the phenotypic heterogeneity between the daughter and father is their difference in disease progression, which correlates with their age difference. IRDs affecting cone cells are commonly categorized into two subgroups: stationary and progressive. Stationary IRDs associated with cone cells usually manifest during infancy and exhibit minimal or no disease progression throughout an individual's lifespan.[23] However, our study's patients deviate from this established pattern. Notably, prior research has also linked *GUCY2D*-associated CORD with progressive symptomatic development.[24]

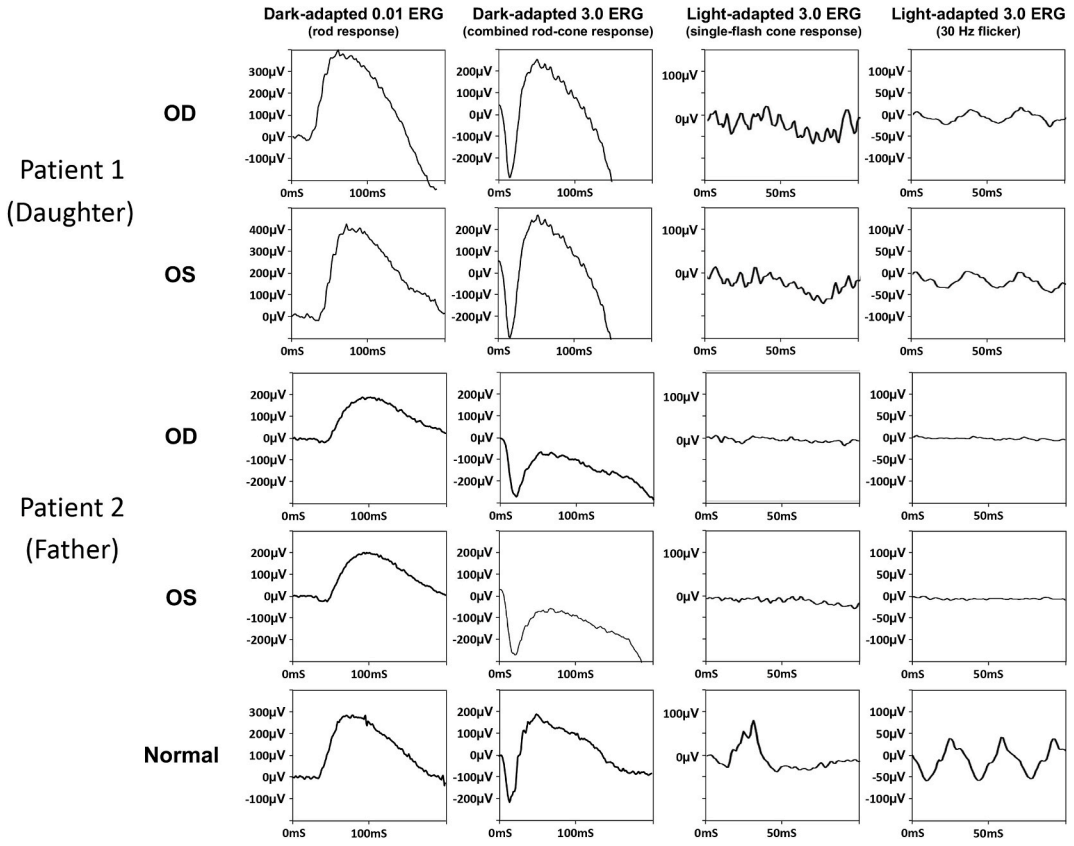

Fig. 4. Full-field electroretinography (ff-ERG) of two patients. Patient 1's ff-ERG revealed a reduced amplitude and delayed implicit times in photopic responses and 30Hz flicker ERG in both eyes. Patient 2's ff-ERG revealed both an implicit time delay in dark-adapted 0.1 ERG in both eyes. Electronegative ERG was present in dark-adapted 3.0 ERG in both eyes. Extinguished response to photopic ERG and 30Hz flicker ERG in both eyes.

Therefore, we propose that both patients exhibit CORD in a progressive pattern related to age, to account for the heterogenic phenotype. A two-phase progression is proposed for progressive CORD. In the first phase, patients experience color vision abnormalities at an early phase. The visual field shows central scotoma and retinal atrophy in the macular in their fundus image. Additionally, their ERG might exhibit a slight shift in the implicit time of cone response. In the second phase, night blindness becomes more apparent for patients, while experiencing nystagmus. Their ERGs might also show abnormalities of the rod cell responses.[10,25] Previous studies concerning *GUCY2D*-associated AD-CORD patients have reported similar results to ours. Decreased VA, loss of photopic function, and central scotoma were observed during childhood. The conditions gradually worsened, progressing into peripheral vision loss, night blindness, and extinguished ERG responses by their 40s.[24] Possible explanations could include the difference between their ages. Patient 1 might still be in the first phase of CORD while patient 2 has already progressed into the second phase. The results suggest even patients carrying the same pathogenic genetic variant could display variant clinical phenotypes due to factors such as age, which is related to their disease progression.

It is worth noting that patient 2 was found to have electronegative dark-adapted 3.0 ERG. Electronegative ERG is defined as a selective reduction in the b-wave amplitude and that it does not exceed that of the a-wave.[26] CSNB caused by *GUCY2D* variants was unlikely in patient 2 due to the autosomal dominant variant. In addition, both patients' fundus examinations showed macular lesions. An electronegative ERG usually indicates that there is retinal dysfunction occurring post--phototransduction.[18] Patient 2's electronegative ERG with a reduction in b-wave amplitude suggested that there might be a dysfunction in the inner retinal, possibly bipolar cells, or the photoreceptor synapse. Previous studies have also reported electronegative dark-adapted 3.0 ERG in AD-CORD patients with p.Arg838Cys and p.Glu837Asp variants in *GUCY2D*.[3,7,21] Along with our study, these cases suggested that electronegative ERG may not necessarily be an inevitable outcome of the advanced disease stage. Also, patients had a wide age range, so factors other than age progression should be considered. Earlier research identified the activation of retinal guanylate cyclase through its cytoplasmic domain, where processes like dimerization and the binding of guanylate cyclase-activating protein 1 (GCAP-1) occur.[27] The p.Arg838Cys variant position occurs within this region of the protein. One plausible hypothesis suggests that GCAP-1, which is localized in the synaptic layer of the photoreceptor,[14,28] might be unable to bind to the mutant retinal guanylate cyclase, thereby affecting synaptic communication with the second-order cells, such as bipolar cells and Müller cells. This explanation is corroborated by findings presented by Gregory-Evans et al.[3] Given that GCAP-1 and Ret-GC are mainly expressed in the outer segments of cone cells rather than the synaptic region,[28] this could clarify why an electronegative ERG pattern may be found in some but not all *GUCY2D*-associated AD-CORD patients.

Electronegative ERG in AD-CORD patients is not exclusive to those with *GUCY2D* mutant patients. Genes such as cone-rod homeobox (*CRX*), peripherin 2 (*PRPH2*), and retina and anterior neural fold homeobox 2 (*RAX2*) have also been associated with this phenomenon. *CRX* encodes a protein that functions as a transcription factor involved in maintaining photoreceptor integrality.[29] Studies have identified *CRX* variants as a pathogenic gene variant causing AD-CORD (MIM # 120970). Among those variants, some studies have reported the presence of electronegative ERG patterns alongside the disease.[30–32] Electronegative ERG has also been recognized as one of the most sensitive biomarkers for *CRX*-linked AD-CORD,[31] indicating a dysfunction in communication between photoreceptors and secondary neurons. *PRPH2*, which encodes the protein peripherin 2, plays an important role

in the formation and renewal of the outer segments of photoreceptors.[33] Multiple studies have reported *PRPH2*-linked AD-CORD (MIM #608161) cases with electronegative ERG,[34,35] although conflicting results have also been documented.[36] The protein encoded by *RAX2* functions as a transcription factor during photoreceptor development.[37] Patients with *RAX2*-linked AD-CORD (MIM #610381) have also been noted to exhibit electronegative ERG.[36] All the genes mentioned above, including *GUCY2D,* are predominantly expressed in the outer segment of photoreceptors, making it rare for variants in these genes to lead to electronegative ERG. Per our hypothesis for *GUCY2D*, we believe that these gene variants might also lead to dysfunction at the synaptic junction, thereby interfering with the communication between photoreceptors and their adjacent secondary neurons.

4. Conclusions

In this study, we identified 2 patients, a daughter, and her father, with the same heterozygous variant in the *GUCY2D* gene linked to AD-COD and AD-CORD. Despite sharing the same pathogenic variant, the disease exhibited heterogeneous clinical phenotypes as factors such as age and progression rate could be involved in disease progression. It's noteworthy that patients with identical genetic variants might present varying rates of disease progression. Patient 2, who also had an electronegative ERG pattern, led us to attribute this response to a dysfunction at the synaptic junction between photoreceptors and secondary neurons caused by the *GUCY2D* variant. We report an electronegative ERG in a patient with p.Arg838Cys *GUCY2D* variant associated AD-CORD, which to the best of our knowledge, has been infrequently reported in past cases. Electronegative ERG was also evident in other gene-associated AD-CORD. We believe that a similar hypothesis could be applied to explain this phenomenon.

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5. Patient consent

The patients were informed and consented to the publication of the case report.

6. Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Pei-Liang Wu: Writing – review & editing, Writing – original draft, Visualization, Validation. **Pei-Hsuan Lin:** Writing – review & editing, Validation, Supervision, Conceptualization. **Winston Lee:** Writing – review & editing, Validation, Supervision, Conceptualization. **Ethan Hung-Hsi Wang:** Writing – review & editing, Visualization, Validation, Supervision. **Eugene Yu-Chuan Kang:** Writing – original draft, Validation, Supervision, Conceptualization. **Laura Liu:** Writing – review & editing, Validation, Supervision, Conceptualization. **Nan-Kai Wang:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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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