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A novel mutation in the *NR2E3* gene associated with Goldmann-Favre syndrome and vasoproliferative tumor of the retina

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Purpose: Various autosomal recessive retinal dystrophies are reported to be associated with mutations in nuclear receptor subfamily 2, group E, member 3 (*NR2E3,* also called *PNR*) gene. The present study proposed to understand the clinical and genetic characteristics of the family of a patient with an ocular phenotype consistent with Goldmann-Favre syndrome (GFS) and vasoproliferative tumors of the retina (VPTRs).
Methods: Twelve family members of the proband from three generations underwent complete ophthalmic examination, including best-corrected visual acuity with Snellen optotypes, tonometry, biomicroscopic examination, indirect ophthalmoscopy after pupillary dilatation, computerized perimetry, optical coherence tomography, fundus photography, intravenous fluorescein angiography, and electroretinography (ERG). All the study subjects underwent genetic analysis of the entire coding region of the *NR2E3* gene with the bidirectional DNA sequencing approach. Hundred healthy individuals were screened for the variant.
Results: The phenotype of the proband had features of GFS with VPTRs. The tumors showed complete resolution with cryotherapy and transpupillary thermotherapy (TTT). Sequencing of the entire coding region of the *NR2E3* gene in the proband revealed a novel homozygous c.1117 A>G variant that led to the amino acid change from aspartic acid to glycine at position 406 (p.D406G). This change was present in the homozygous state in affected family members and in the heterozygous state in unaffected family members, and was undetectable in the control subjects. The identified novel p.D406G homozygous mutation was at an evolutionarily highly conserved region and may possibly affect the protein function (Sorting Intolerant From Tolerant [SIFT] score = 0.00).
Conclusions: Patients with GFS may present with retinal VPTRs that respond to therapy with cryotherapy and TTT. Molecular genetic studies helped to identify a novel p.D406G mutation in the affected members, which will aid in confirming the diagnosis, for genetic counseling of family members and potentially provide some form of therapy for the affected patients.

Goldmann-Favre syndrome (GFS) is a vitreoretinal dystrophy that manifests with early onset of night blindness, atypical pigmentary dystrophy of the retina, degenerative changes in the vitreous humor, peripheral and, less often, central retinoschisis, lens opacities, and an enhanced S-cone response on electroretinography (ERG) [1]. Various autosomal recessive retinal dystrophies including enhanced S-cone syndrome (ESCS), GFS, and clumped pigmentary retinal degeneration have been described as associated with mutations in nuclear receptor subfamily 2, group E, member 3 (*NR2E3* also called PNR [NCBI Reference Sequence: NM_014249.3]) gene [2–5]. The *NR2E3* gene codes for a nuclear receptor that is specific to photoreceptors [2]. A common feature of these syndromes is a unique abnormality on ERG of absent rod activity and large S cone–mediated responses under photopic and scotopic conditions, known as the enhanced S-cone response [6].

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Vasoproliferative tumors of the retina (VPTRs) are benign tumors of retinal vascular origin. These masses may be idiopathic or secondary to predisposing conditions such as intermediate uveitis, retinitis pigmentosa, ocular toxocariasis, Coats disease, chronic retinal detachment, and other traumatic or inflammatory diseases [7-10].

We report a patient with clinical features of GFS with secondary VPTRs successfully treated with a combination of transpupillary thermotherapy (TTT) and cryotherapy. The molecular genetic evaluation of the family revealed a novel mutation in the *NR2E3* gene. To our knowledge, this is the first report of VPTRs in association with GFS, and the VPTRs successfully resolved with TTT and cryotherapy.

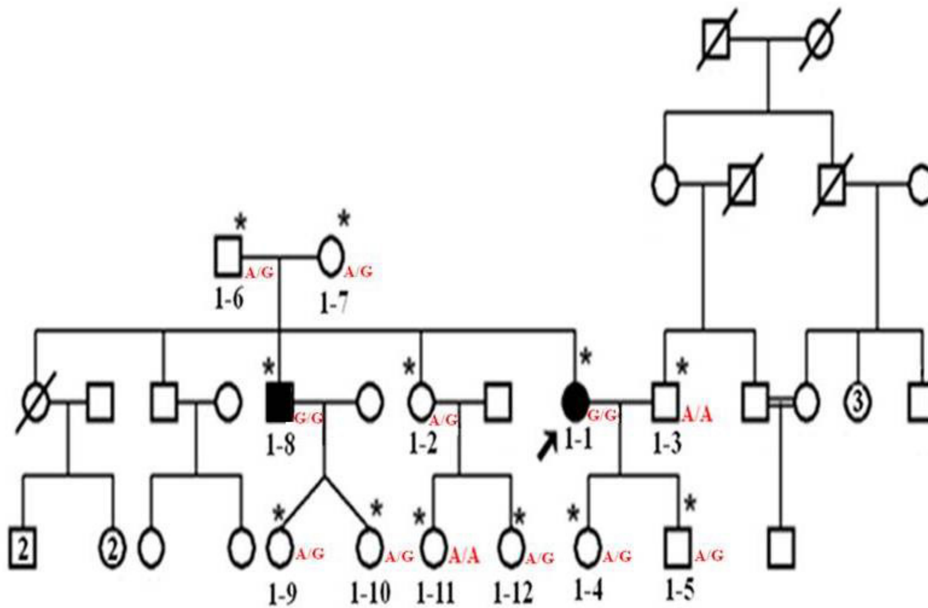

Figure 1. Pedigree of the family in this study. The asterisk symbol represents the sequenced individuals in this study. The genotyping of alleles were shown below the individuals.

METHODS

The study was performed after receiving approval from the institutional ethics review board and in accordance with the Declaration of Helsinki. The nature of the study was conveyed, and informed consent was obtained from all study subjects. We certify that all applicable institutional and government regulations concerning the ethical use of human volunteers were followed during this research. The proband along with 11 family members from three generations were included in the study (Figure 1).

Ophthalmological and electrophysiological studies: All study subjects underwent a complete ophthalmic examination that included evaluation of best-corrected visual acuity (BCVA) with Snellen optotypes, Goldman applanation tonometry, biomicroscopic examination, indirect ophthalmoscopy after pupillary dilatation, computerized perimetry, optical coherence tomography (OCT; Zeiss Cirrus HD OCT –4000, Carl Zeiss meditec, Inc. Dublin, CA), fundus photography (TOPCON TRC 50 DX), and intravenous fluorescein angiography (IVFA; TOPCON TRC 50 DX, Tokyo, Japan). ERG (LKC Technologies, Gaithersburg, MD) was performed according to standard testing protocols recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV).

Molecular genetic studies: A detailed family history and pedigree was constructed. One hundred unrelated ethnic- and age-matched control subjects were recruited for this study.

Sample collection and DNA preparation: Approximately 5 ml intravenous blood was collected in a anticoagulant (EDTA) coated tubes from all 12 study subjects and 100 Indian controls. Genomic DNA was prepared from peripheral blood leukocytes with salting-out method [11], by dehydration and precipitation of cellular proteins in a saturated sodium chloride solution. The isolated DNA will be dissolved in TE buffer (1 M Tris-pH 8.0; 0.5 M EDTA-pH 8.0) and stored at -20 °C until use.

Polymerase chain reaction and DNA sequencing: Eight sets of primers were used to amplify the entire coding region of *NR2E3* gene [12]. The PCR products were gel eluted and column purified using an EZ-10 spin-column DNA gel extraction kit (Bio Basic, East Markham, Canada). A total of 20 µl master mix was prepared using 50–100 ng of genomic DNA, 1×PCR buffer, 200 µM of dNTPs (Medox Biotech India Pvt. Ltd, Chennai, India), 50% dimethyl sulphoxide (DMSO; Merck, Mumbai, India), 0.25 picomoles of each primer, and 1 unit of Taq DNA polymerase (Sigma, Saint Louis, MO), to perform PCR. The conditions followed were initial denaturation at 95 °C for 5 min, followed by 32 cycles (95 °C for 30 s, 55 °C for 30 s, and 72 °C for 1 min) and final extension at 72 °C for 10 min. Bidirectional sequencing was performed using the ABI 3130 genetic analyzer (Applied Biosystems, Foster City, CA) with dye- termination chemistry.

Bioinformatics assessment: The evolutionary conservation of the identified *NR2E3* mutation was checked using the clustalW multiple sequence alignment tool. Sorting Intolerant From Tolerant (SIFT) was used to assess the likely phenotypic

effect of the identified missense mutation. PolyPhen analysis was performed to calculate the probability of the identified mutation being deleterious toward disease pathogenesis.

RESULTS

Patient 1: The proband on presentation had a BCVA of perception of light in the right eye (RE) and 6/12 in the left eye (LE). Anterior segment examination of the RE showed severe corneal edema, neovascularization of the iris, posterior subcapsular cataract, and intraocular pressure (IOP) of 50 mmHg suggestive of neovascular glaucoma, and the LE showed a clear cornea and mild lens opacities due to posterior subcapsular cataract. The RE fundus details were not clearly visible through the hazy media due to corneal edema and lenticular opacity. However, peripheral retinal exudation and mass lesions similar to those in the LE could be seen hazily. The LE fundus examination showed vitreous degenerative changes, a healthy optic disc, and nummular pigment clumps at the level of the RPE in the midperiphery and along the vascular arcades, associated with diffuse RPE atrophy. The opaque, white dendritic appearance of the peripheral vessels was present throughout the midperiphery with mild arterial attenuation (Figure 2A). Three raised dome-shaped, yellowish-pink, vascular masses 4 DD in extent were noted in the peripheral retina in the superior, superotemporal, and inferotemporal quadrants. These masses were associated with subretinal exudation (Figure 2B,C). No dilated or tortuous feeder vessels were noted. IVFA showed rapid filling of the dye in the early phase, with the lesions becoming increasingly hyperfluorescent and leaking diffusely in the late phase. Telangiectatic and dilated vessels were observed within the tumor masses (Figure3). Full-field ERG showed a severe decrease in the rod and cone responses in both eyes (BE). Based on the clinical, angiographic, and electrophysiological findings, a diagnosis of secondary VPTRs associated with retinal dystrophy was made. All the tumors were treated with transpupillary thermotherapy (TTT) in two sittings. Peripheral tumors were treated with cryotherapy with the triple freeze thaw technique. Complete regression of the vascular masses was noted over 6 months (Figure 2D), and the final BCVA was 6/9 in the LE. Notably, there was an absence of macular or peripheral retinal schisis in this patient.

Patient 2: The 43-year-old healthy elder brother of our proband had complained of defective night vision since childhood.

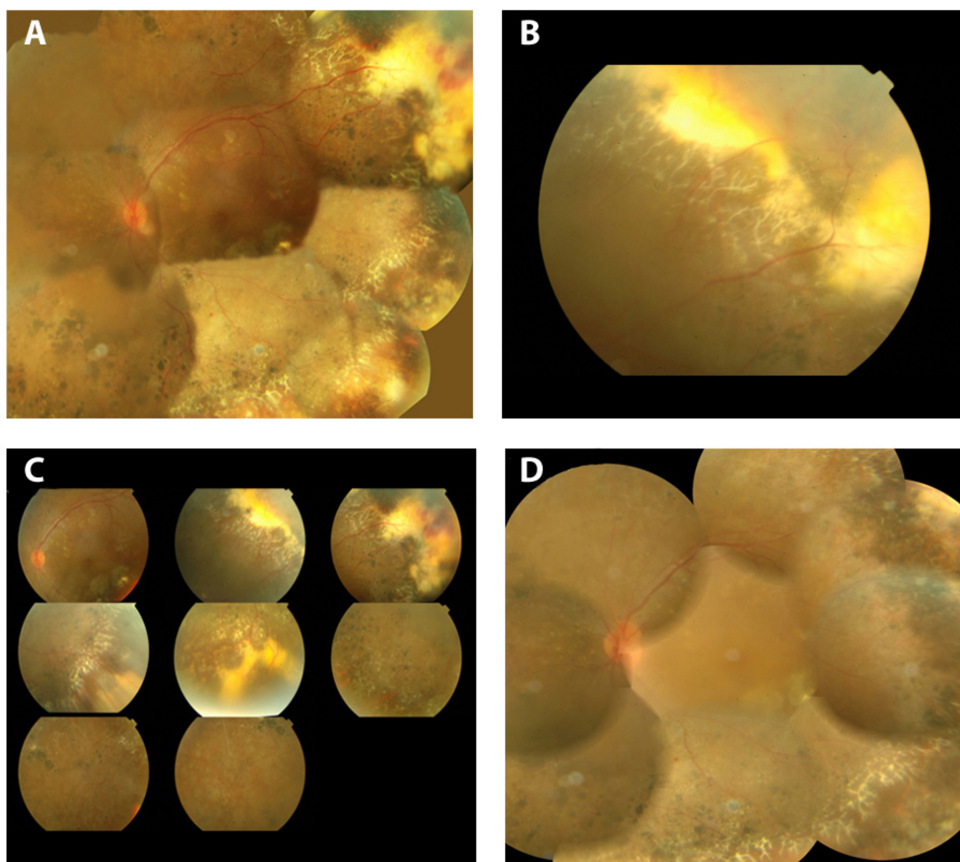

Figure 2. Pre and Post treatment LE color fundus photograph of the proband **A**: Pre-treatment montage fundus photograph of left eye. LE Fundus shows a healthy appearing optic nerve head with diffuse RPE degeneration with nummular pigment clumps and white dentritic peripheral vessels in mid peripheral region . Vascularized tumor mass with exudation and absent feeder vessels is seen in the supro-temporal periphery. **B**: Vascularized peripheral tumor with profuse exudation. **C**: 9 Up fundus photograph of LE showing vasoproliferative tumors with exudation in superior, suprotemporal, inferotemporal and inferior quadrants. **D**: Post-treatment fundus photograph. LE fundus showing complete regression of the tumor masses with treatment. (6 month post treatment).

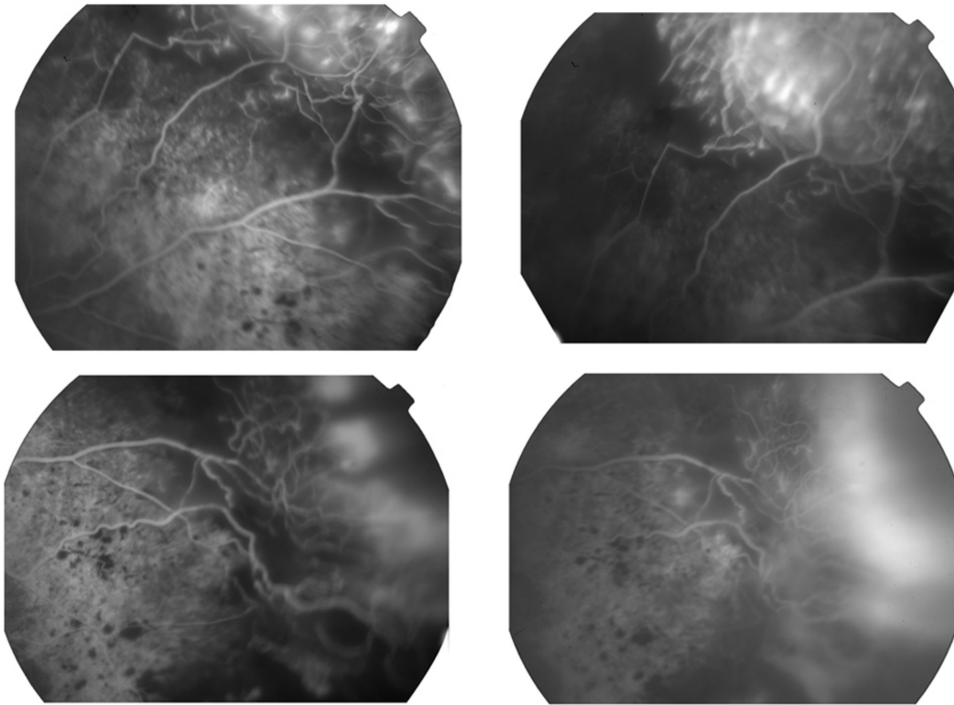

Figure 3. Fundus fluorescein angiography of vasoproliferative tumor. FFA shows rapid filling of the dye in the early phase, with the lesion becoming increasingly hyperfluorescent, and profuse and diffuse leakage of dye in the late phase of angiogram.

His BCVA was 6/6 BE. Anterior segment examination was normal. Dilated fundus examination showed a healthy optic disc and normal caliber of the retinal vessels. There was a mild diffuse RPE change with few pigment deposits in the midperipheral and peripheral retina. ERG showed decreased rod-specific responses, the response to a standard flash was delayed with low amplitude waveform under photopic and scotopic conditions, and the 30 Hz flicker response was delayed and of decreased amplitude. The responses to long duration stimulus using a blue flash with orange background (S-cone ERG response) showed an abnormally large delayed waveform typical of the enhanced S-cone response (Figure 4A,B). Ocular history and examination of the other ten members of the family were unremarkable.

The findings of the clinical, angiographic, and electrophysiological examinations suggested a possible diagnosis of GFS. Thus, full sequencing of the *NR2E3* gene was undertaken in the proband. This revealed a novel, homozygous c.1117 A>G variant in exon 8 of the gene, a substitution mutation. This change leads to an amino acid change (aspartic acid to glycine) at position 406 of the gene. The p.D406G change was detected in the homozygous state in the proband's brother (affected) and in the heterozygous state in eight unaffected family members (Figure 5; Table 1).

Screening of the *NR2E3* gene in 100 unrelated Indian control samples of the same ethnic background did not show the p.D406G variant. The identified novel p.D406G homozygous mutation was evolutionarily highly conserved in different species (Figure 6). The SIFT score was 0.00, and the PolyPhen score was 0.998. These features suggest the pathologic nature of the identified genetic variation.

DISCUSSION

Patients with GFS typically present with early onset night blindness, atypical pigmentary retinal dystrophy, degenerative changes of the vitreous, peripheral or macular retinoschisis, lens opacities, and characteristic ERG abnormalities [1]. The presenting features and findings of the ophthalmic examination in the proband in this study led to the clinical diagnosis of GFS. Although ERG responses were severely reduced in the proband due to advanced disease, the proband's brother displayed a hypersensitive response to blue light. The maximal response to short wavelengths, virtually no change in the response waveform to light and dark adaptation, some long- and middle-wavelength–sensitive cone dysfunction, and high subjective S-cone spectral sensitivity has been demonstrated in patients with GFS, and is termed the enhanced S-cone response [1,2].

The *NR2E3* gene responsible for causing ESCS is located on chromosome 15q23 [12]. The gene coding region contains eight exons and spans a 7 kb region [13]. The gene contains the DNA-binding domain (DBD) at the N-terminus end and

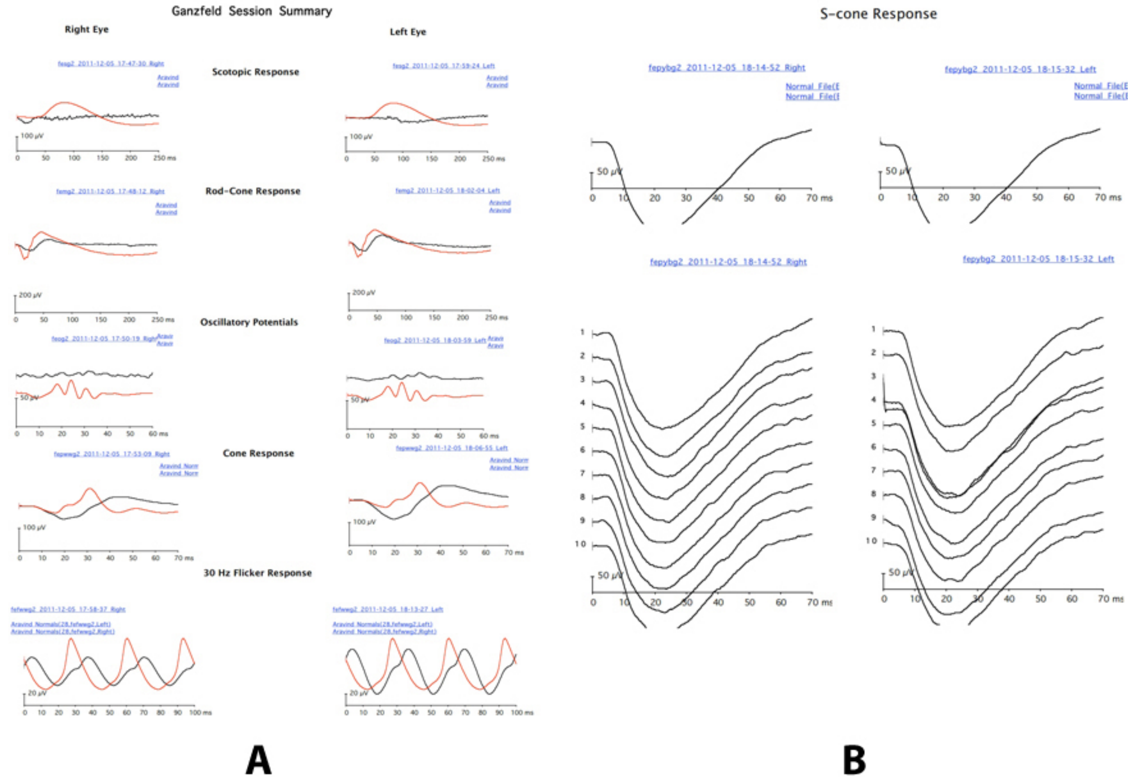

Figure 4. Electroretinography and S-Cone ERG findings in case 2. **A**: ERG findings in case 2. ERG shows severely reduced rod specific responses, response to standard flash was delayed with low amplitude waveform under photopic and scotopic conditions, the 30 Hz flicker was delayed and of lower amplitude. **B**: S-Cone ERG with blue flash and orange background showing abnormally large, delayed, simplified waveform as enhanced S cone ERG responses.

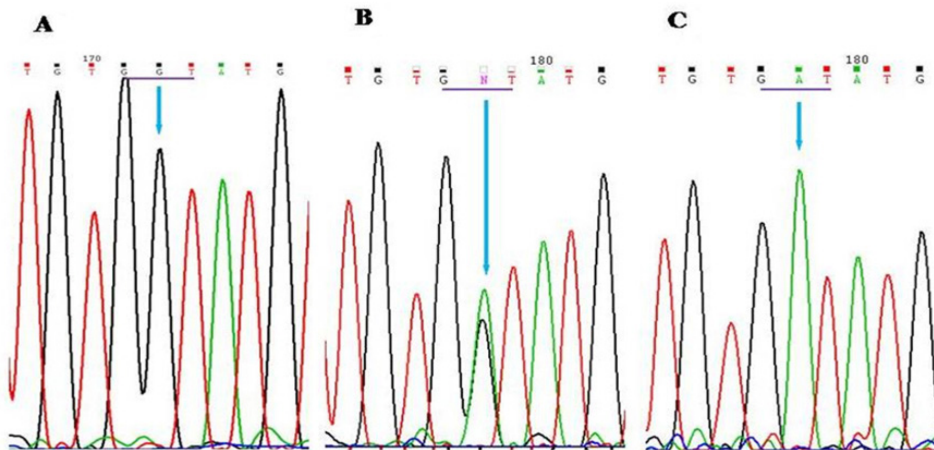

Figure 5. Chromatogram representing the p.Asp406Gly mutation in the *NR2E3* gene. **A**: p.Asp406Gly mutation in the homozygous state. **B**: p.Asp406Gly mutation in the heterozygous state. **C**: Wild type. The underline marks the mutated codon. The arrow indicates the position of the mutation.

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>gi|7657395|ref|NP_055064.1| [Homo sapiens]                        402 KLLCDMFKN 410
>gi|114657918|ref|XP_001175025.1|[Pan troglodytes]                 394 KLLCDMFKN 402
>gi|109081780|ref|XP_001089693.1| [Macaca mulatta]                 440 KLLCDMFKN 448
>gi|269315847|ref|NP_001161372.1|[Bos taurus]                      403 KLLCDMFKN 411
>gi|7305323|ref|NP_038736.1|[Mus musculus]                         387 KLLCDMFKN 395
>gi|45382987|ref|NP_989925.1|[Gallus gallus]                       398 KLLCDMFKN 406
>gi|55925261|ref|NP_001007369.1|[Danio rerio]                      411 KLLCDMFKN 419
>gi|221330285|ref|NP_611032.2|[Drosophila melanogaster]            574 KVLCDMYKN 582
>gi|158298860|ref|XP_319009.4|[Anopheles gambiae str. PEST]        518 KVLCDMYKN 526
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Figure 6. Evolutionary conservation of p.Asp406Gly (D406G) mutation in different species. Amino acid residues highly conserved in all species are indicated by asterisk, and lower identity are shown using colon. Red color box indicate *NR2E3* mutations analyzed in this study.

ligand-binding domain (LBD) at the C-terminus end. Most of the human *NR2E3* variants and mutations are identified in these two domains [14]. In the present study, we identified a novel mutation in the LBD of the C-terminus end.

Thus far, nearly 50 *NR2E3* gene variations and mutations have been reported in patients with various retinal degenerative disorders. Gerber et al. identified a p.R311Q mutation in the *NR2E3* gene in the patients who may have ESCS [15]. Later, Haider et al. reported the same p.R311Q mutation with 44.8% frequency in patients with ESCS [12]. This same p.R311Q mutation in the *NR2E3* gene was also reported with homozygosity in a patient with GFS [16]. In our study, we identified a novel p.D406G (c.1117A>G) mutation with homozygous state in the patient and in the affected sibling.

The variability of clinical features and the severity of retinal degeneration produced by *NR2E3* mutations may often complicate the diagnosis. Patients with *NR2E3* mutations may show characteristic features of GFS, as in our patient, or may have the ERG pattern typically seen in ESCS or clumped pigmentary retinal degeneration.

To our knowledge, the p.D406G homozygous mutation is novel. It was not seen in any of the control samples screened. The p.D406G homozygous mutation was also observed in the proband's brother who has clinical features in a less severe form and did not show the presence of VPTRs. Both parents of the proband were heterozygous for the p.D406G mutation, which indicates that the parents were carriers for the disease and transferred the risk allele (G) to the proband. Out of the 12 family members who participated in this study, only two carry the normal allele (A). The remaining family members carry the risk allele with heterozygosity (A/G) that indicated they are carriers for the disease. A similar condition was reported by Haider et al., in the ESCS case. The p.M407K mutation was observed with the homozygous condition in the

Table 1. Genotype of the family members in the study.

Individual ID	Age /Sex	Family member's relation with the Proband	Disease state	Genotype	Genotype Status
1–1	40/F	Proband	Affected	GG	Affected homozygote
1–2	41/F	Sister	Normal	AG	Carrier heterozygote
1–3	48/M	Husband	Normal	AA	Normal homozygous
1–4	12/F	Daughter	Normal	AG	Carrier heterozygote
1–5	14/M	Son	Normal	AG	Carrier heterozygote
1–6	75/M	Father	Normal	AG	Carrier heterozygote
1–7	70/F	Mother	Normal	AG	Carrier heterozygote
1–8	42/M	Brother	Similar clinical features of proband	GG	Affected homozygote
1–9	9/F	Brother's daughter	Normal	AG	Carrier heterozygote
1–10	9/F	Brother's daughter	Normal	AG	Carrier heterozygote
1–11	16/F	Sister's daughter	Normal	AA	Normal homozygous
1–12	13/F	Sister's daughter	Normal	AG	Carrier heterozygote

The p.D406G change is detected in the homozygous state in the proband and proband's brother and in the heterozygous state in eight unaffected family members.

patient, whereas two unaffected siblings carry the risk allele with heterozygous condition in their study [12].

Atsuhiro Kanda et al. showed that the *NR2E3* sequence is highly conserved during evolution and the residue p.M407K was conserved in all *NR2E3* orthologs [14]. The identified p.D406G mutation in the proband was also highly conserved during evolution (Figure 6).The SIFT score (0.00) showed that this mutation affected the protein function. The PolyPhen analysis also predicted that this mutation probably damaging the protein function with a score of 0.998. The amino acid aspartic acid/aspartate that is acidic polar and has been changed by the substitution of a nonpolar amino acid glycine at the 406 conserved position might have altered the *NR2E3* protein structure and led to the disease occurrence in this case. The SIFT and PolyPhen scores support the deleterious nature of the p.D406G mutation. Further functional studies are required to confirm the pathogenesis of the p.D406G mutation.

VPTRs may be primary or secondary. In the largest review of 295 patients with 334 VPTRs by Shields et al. in 2012, 80% were idiopathic, and 20% were secondary. The most common preexisting ocular disease included retinitis pigmentosa (22%), pars planitis (21%), Coats disease (16%), previous retinal detachment surgery (12%), idiopathic peripheral retinal vasculitis (6%), and familial exudative vitreoretinopathy (4%). Other retinal lesions that might predispose to the development of VPTRs include toxoplasmic retinitis, toxocariasis, and traumatic choroidopathy [8]. A literature review showed no previous documentation of VPTRs in patients with GFS.

Primary tumors tend to be solitary, small, and located near the inferotemporal portion of the fundus. Secondary VPTRs are more often multifocal, bilateral, and believed to be a reactive vascular response to various ocular insults. The vascularized retinal nodules may threaten vision due to retinal exudation, macular edema, intraretinal or vitreous hemorrhage, and formation of epiretinal membranes [8]. These benign but vision-threatening tumors have been shown to respond to various treatment modalities such as cryotherapy, TTT, brachytherapy, and tumor resection [9]. The proband lost vision in her RE due to neovascular glaucoma (NVG) secondary to VPTRs, a described complication of VPTRs [8]. The tumors in the LE were treated with TTT (posterior tumors) and cryotherapy with the triple freeze thaw technique (extreme peripheral tumors). Complete regression of the vascular masses in our patient was observed within 6 months.

Retinoschisis, a feature of GFS, was not seen in our patient. However, the distinctive ophthalmoscopic feature is nummular pigmentary deposition at the level of the RPE, usually located in the midperiphery and often associated with RPE atrophy. This characteristic pigmentary clumping was noted in our proband, along with degenerative vitreous changes, lenticular opacity, and the abnormal ERG pattern. In our patient, opaque white dentritic retinal vessel changes were present throughout the midperiphery extending anteriorly between the equator and ora serrata. Since the fundus features vary among patients, Fishman et al. concluded that a diagnosis of GFS should be considered in patients presenting with an early history of poor night vision, bilateral atypical pigmentary changes in the retina, and degenerative changes in the vitreous humor. Additional diagnostic findings include retinoschisis, opaque dentritic retinal vessels, diffuse leakage from retinal capillaries, and cystoid macular edema [1]. Molecular genetic testing is essential for establishing the correct diagnosis in patients with *NR2E3* mutations because of the variable phenotype associated with these degenerations. Further research may shed light on the association between the genetic mutation seen in our family with the observed phenotype.

In conclusion, we have described a heretofore unreported association of retinal VPTRs in GFS. The tumors regressed with standard treatment modalities. Detection of a novel p.D406G mutation in the *NR2E3* gene helped to confirm the diagnosis. Genetic testing also helped in detecting the presymptomatic carrier and thus proved to be of immense value in informed genetic counseling of the family members and would potentially provide some form of therapy for the affected patients.

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