Multimodal imaging and genetic screening in Mexican patients with Gyrate Atrophy. Identification of novel OAT pathogenic variants.

Ana Lía Díazceballos-García (✉ analiadiazceballos@gmail.com)
  Institute of Ophthalmology

Rodrigo Matsui
  Institute of Ophthalmology

María Graciela Chairez Miranda
  Institute of Ophthalmology

Jaime Francisco Rosales Padrón
  Institute of Ophthalmology

Federico Graue-Wiechers
  Institute of Ophthalmology

Juan Carlos Zenteno
  Institute of Ophthalmology

Case Report

Additional Declarations: No competing interests reported.

Abstract

Purpose

Description of retinal phenotype by structural and functional testing, ornithine plasma levels and mutational data of *OAT* gene in patients with Gyrate Atrophy (GA).

Methods

Ophthalmologic examination, fundus photography (CFP), autofluorescence (FAF), spectral-domain optical coherence tomography (SD-OCT), Goldmann perimetry (GP), full-field electroretinogram (ffERG) and chromatic perimetry (CP) testing were performed. Ornithine plasma levels were measured. Sanger sequencing mutational analysis of the coding exons and exon-intron junctions of the *OAT* gene were analyzed.

Results

Twelve eyes of seven Mexican patients with GA were included. CFF showed peripheric patches of chorioretinal atrophy; FAF revealed peripheric oval areas of hypoautofluorescence; SD-OCT exhibited outer retinal tubulations in 58%, cystoid macular edema in 50%, epiretinal membrane in 42%, foveoschisis and staphyloma in 17%, and hyperreflective deposits in 100% of the eyes; GP showed constricted visual fields in 100% of the eyes; ffERG revealed preserved photopic response in 17% and preserved scotopic response in 17% of the eyes; CP exposed a deficit in generalized response of rods and cones in 100% of the eyes. Mean ornithine plasma levels were 509.5 µmol/L. One patient with genetic confirmation of GA had normal ornithine plasma levels (48 µmol/L). Molecular findings in OAT gene detected two novel pathogenic variants: c.796 C > T (p.Gln266*) and c.721_722dupCC (p.Asp242ArgfsTer6).

Conclusion

This study provides new information regarding functional and structural diagnosis in patients with GA, expands the understanding of retinal phenotype in patients with GA, reports two novel mutations and presents the first case of GA confirmed by genetic testing with normal ornithine levels.

Introduction

In 1896, E. Fuchs described for the first time a progressive degeneration of the retina and choroid in young patients which was named "atrophia gyrata chorioideae et retinae"(1); since then, this rare autosomal recessive chorioretinal dystrophy has been widely studied, exhibiting variable clinical characteristics (2). To date, more than 200 individuals with Gyrate Atrophy (GA) have been reported in the literature, of which one third corresponds to the Finnish population. Chorioretinal atrophy in GA is generated by increased levels of ornithine due to a deficiency of ornithine-δ-aminotransferase (OAT) which normally removes ammonia from the cells by the conversion of L-ornithine to proline and glutamic acid (3, 4, 5). GA is caused by biallelic mutations in the *OAT* gene, with more than 60 different mutations reported to date in individuals from diverse ethnic origins and

with no apparent genotype–phenotype correlation (6). GA is clinically characterized by night vision impairment and loss of peripheral visual field starting in the first and second decades of life. In addition, myopia, cataracts and cystoid macular edema (CME) are common early features (7). Initial fundoscopic changes are well described as round sharply defined areas of retinal and choroidal atrophy in the periphery and equator which in late stages tend to coalesce and spread centripetally (5, 7–10). These lesions lead to a marked separation between healthy/normal and atrophic retina with loss of external layers, retinal pigment epithelium, choriocapillaris and most of the medium and large choroidal vessels (11). Studies in GA mouse models and humans have demonstrated that early correction of ornithine levels, being abnormally elevated up to 20-fold in typical cases, can slow long-term progression of the retinal degeneration (12–13). Dietary plans including restricting arginine and low protein intake adding or not supplementations such as vitamin B6 or l-lysine, have been reported useful to lower and stabilize ornithine levels showing good results in vision improvement and slowing the progression. (2, 14–18). While some case reports and a few case series of GA patients from diverse ethnic groups have been clinically and molecularly characterized (16–17, 19–21) no information from Latin American patients do exist.

The aim of this study is to describe the retinal phenotype by functional and structural retinal testing in a Mexican cohort of patients diagnosed with GA and to report the pathogenic *OAT* variants identified in them. This is the first case series of GA reported in the Mexican population and our results expand the understanding of retinal phenotype and the mutational spectrum associated with GA.

Methods and Materials

The study was approved by the Institutional Ethics Committee of the Institute of Ophthalmology "Conde de Valenciana" in Mexico City and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The inclusion criteria included patients with clinical characteristics of GA and clear media that allowed adequate clinical and multimodal imaging evaluation of the eye. Patients with suspected GA but no mutation in OAT gene were excluded.

Clinical ophthalmological evaluation:

The patients were evaluated at the Clinic for Inherited Retinal Degenerations of the Institute of Ophthalmology Conde de Valenciana by a retina specialist by means of a full ophthalmological evaluation that included slit lamp examination, intraocular pressure measurement by applanation tonometry, and dilated funduscopic evaluation. Demographic data as well as a complete clinical questionnaire were reported. All patients underwent best-corrected visual acuity measurement (BCVA) using Snellen Chart and then converted to Logarithm of Minimum Angle of Resolution (logMAR) values.

Structural retinal evaluation:

Wide Field Color Fundus Photography (CFP) (Optos California, USA) and a 55 grade Color Fundus Photography (Spectralis; Heidelberg Engineering GmbH; Heidelberg, Germany) or a 45 grade Color Fundus Photography (DRI OCT Triton, Swept source OCT, TOPCON Corporation; Tokyo, Japan) were taken to each patient. To estimate retinal pigment epithelium (RPE) status, retinal autofluorescence (FAF) was obtained using the 488 nm (Spectralis; Heidelberg Engineering GmbH; Heidelberg, Germany) and the 532 nm (Optos California, USA)

imaging softwares. Retinal horizontal and vertical cross-sections were obtained with the spectral domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering GmbH; Heidelberg, Germany). A 9-mm line scan along the horizontal and vertical meridians crossing the fovea was performed in all patients. The total area of the outer nuclear layer (ONL) in both meridians crossing the fovea, the subfoveal ONL thickness in the horizontal meridian, and the eccentricity of the ellipsoid zone (EZ) line in both meridians were determined by manual segmentation using the Spectralis built-in measurement software.

Functional retinal evaluation:

Goldmann kinetic perimetry (GP) was performed in all patients without nystagmus (MonCvONE, Metrovision; Pérenchies, France). Full field ERG (ffERG) (MonPackONE, Metrovision; Pérenchies, France) was performed in all patients using the International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Topographical retinal function of cones and rods were determined by photopic and scotopic visual field testing (Chromatic perimetry; CP) (MonCvONE, Metrovision; Pérenchies, France) under light and dark-adaptation, respectively, in the eye with better BCVA in each patient.

Biochemistry measures:

Blood samples were obtained to quantify ornithine plasma levels in all patients and were analyzed by an independent external laboratory.

Mutation screening of OAT gene:

Genetic analysis was performed at the Laboratory of Molecular Genetics of the Institute of Ophthalmology Conde de Valenciana. For all patients, genomic DNA (gDNA) was extracted from peripheral blood leukocytes using standard methods after obtaining informed consent. The 9 coding exons and exon-intron junctions of the *OAT* gene were amplified by PCR using pairs of primers and temperature conditions available on request. Amplicons were sanger sequenced by the dideoxy chain method using a Compact System Sequencer (Promega, Madison, USA). Obtained OAT sequences were manually compared with the canonical gene transcript NM_000274.4. In compound heterozygous cases, available first relatives were also genetically screened for confirmation of *trans* configuration of the pathogenic variants.

Results

Clinical, structural and functional results:

A total of seven patients (12 eyes) were included in the study, including 4 females and 3 males. The mean age at the time of the first examination was 34.2 years old (age range, 10–66). The mean age of first symptoms reported by the patients were at 9.2 years old (age range, 5–20), being nyctalopia (N = 3) the main visual symptom in 42.8% of the patients as well as blurry vision in 42.8% (N = 3). Associated systemic features included muscle weakness in 29% (N = 2) of patients, cognitive deficit in 14% (N = 1) of patients, and history of otitis media associated and some degree of hearing loss in 29% (N = 2) of patients. 29% (N = 2) of the patients in the study were related (siblings) (P2 and P3). None of the patients were born to consanguineous parents.

Within the ophthalmological clinical findings, the mean BCVA was 0.5 LogMar (range between 0.0−1) (Snellen 20/63; range between 20/20−20/200). 29% (N = 2) of the patients had only one functional eye, one eye had an untreated chronic rhegmatogenous retinal detachment (RRD) with no light perception (P2) and the other eye was eviscerated due to an open ocular trauma (P7). 67% (N = 8) of the eyes had myopia and 50% of the eyes (N = 6) underwent early intervention of cataract surgery (mean age at 20 years). (Table 1)

Table 1
Clinical Characteristics and Ornithine Plasma Levels. *Patients 2 and 3 are sibs.

Patient No.	Gender	Age at Examination (yrs)	Age at Presenting Symptoms	Main Symptom	Visual Acuity (LogMar)		Cataract Surgery		Ornithine in plasma (µmol/L)
					Right Eye	Left Eye	Right Eye	Left Eye	
P1	F	10	6	Visual Field Constriction	0.2	0.1	No	No	916
P2*	M	16	6	Blurry Vision	-	0.2	-	No	552
P3*	M	20	15	Blurry Vision	0	0	No	No	583
P4	F	27	6	Nyctalopia	0.4	0.5	Yes	Yes	636
P5	M	47	20	Nyctalopia	0.9	0.7	Yes	No	48
P6	F	54	7	Blurry Vision	1	1	Yes	Yes	353
P7	F	66	5	Nyctalopia	0.6	-	Yes	-	479

Fundoscopy revealed typical changes of gyrate atrophy in 100% (N = 12) of the eyes, showing sharply demarcated, circular areas of chorioretinal atrophy predominantly distributed in the peripheral retina. 75% (N = 9) of the eyes had macular involvement at the time of the first evaluation of which 25% (N = 3) the fovea was affected. P6 presented a round-shaped atrophic area in the macula with some preserved central foveal tissue with an evident ring-shape area of preserved retina between the coalescent peripheral patches and the posterior pole atrophy. (Fig. 1)

All the patients presented round or oval areas of hypoautofluorescence mainly in the periphery that tend to coalesce, spreading to the macula and partially sparing the peripapillary region, leaving some areas of hyperautofluorescence and also at the border of preserved retina in the macular area. P2 and P3 had an hyperautofluorescent ring outside the arcades separating the posterior retina with normal autofluorescence from hypoautofluorescence in the mid-periphery which did not correspond to the hypoautofluorescence of the patchy atrophic lesions in the far periphery. (Fig. 1)

The structural features of the retina by SD-OCT evaluation demonstrated structural changes that were concordant between eyes in all patients. In the areas of chorioretinal atrophy we found evident thinning of the retina predominantly the external layers with complete loss of photoreceptor inner segment outer segment

junction IS/OS outer retinal as well as the interdigitation zone and external limiting membrane as well as evident choroidal thinning in the most advanced cases, outer retinal tubulations (ORT) were found in 58% (N = 7) of the eyes, cystoid macular edema (CME) was found in 50% (N = 6) of the eyes, 42% (N = 5) of the eyes had an epiretinal membrane (ERM), 17% (N = 2) of the eyes presented foveoschisis and a staphyloma. None of the eyes (N = 0) had focal choroidal excavation. Hyperreflective deposits were found in 100% (N = 12) of the eyes, mainly found in the ganglion cell layer, but also in any layer of the macula in the more advanced cases, with irregular shapes, being most of them round or oval. These lesions were more evident in the two patients with CME, appearing as a band-shape zone in the ganglion cell layer closer to the inner plexiform layer (P4 and P5). (Fig. 1)

The GP test showed constricted visual fields in the isopters I4e and V4e in 100% (N = 12) of the eyes, P3 had an almost preserved V4e visual field in both eyes. P5, P6 and P7 who presented with a more advanced disease had a markedly constricted visual field with a small central visual field in the isopter V4e corresponding to the preserved retina in the fovea. (Fig. 2)

The ffERG revealed a preserved photopic response in 17% (N = 2) of the eyes and a preserved scotopic response in 17% (N = 2) of the eyes. These nearly preserved responses were observed in two of the younger patients (P2 and P3).

Regarding the functional evaluation by the scotopic and photopic visual field test we could see that all of the patients presented some degree of deficit in the generalized response of rods and cones (more evident in the scotopic tests), finding a more reduced response in patients with more advanced disease, in P2 and P3 with a structural well-preserved macula we found an initial but significant mean deficit in the photopic evaluation (cone response) of 25dB and 23dB, respectively, which correlates with the sub-normal findings in the electroretinogram test. (Fig. 2)

Ornithine plasma levels results:

Mean ornithine plasma levels were 509.5 µmol/L, (ranges between 48–916 µmol/L) this reflects an increase of up to more than 4 times its normal value (< 107 µmol/L). *Normal ranges vary between laboratories (22–115 µmol/L are considered normal). An interesting finding is that one patient has ornithine plasma levels within normal ranges (P5). (Table 1)

Molecular findings:

Biallelic OAT mutations were identified in all seven patients, including a pair of affected sibs (P2 and P3). A total of three compound heterozygous and three homozygous phenotypes were identified in the 7 probands. Two novel *OAT* pathogenic variants were identified: c.796 C > T (p.Gln266*) and c.721_722dupCC (p.Asp242ArgfsTer6). The c.721_722dupCC variant was observed in 6 out of 12 pathogenic alleles in our cohort. The most commonly mutated OAT exon in our series was exon 6, harboring 9 out of all 12 disease-causing variants. All three cases of compound heterozygosity demonstrated to carry biallelic OAT mutations (trans configuration) by genetic screening of first-degree relatives (data not shown). Two previously identified mutations in OAT, c.991C > T(p.Arg331*) and c.677C > T (p.Ala226Val) were also recognized. (Table 2)

Table 2
OAT pathogenic variants identified in Mexican GA patients. Two novel mutations were identified. *Patients 2 and 3 are sibs.

PATIENT No.	AGE	EXON	OAT VARIANT	ZYGOSITY	ACMG CLASSIFICATION	REFERENCE
P1	10	6	c.721_722dupCC; p.Asp242fsTer	Homozygous	Pathogenic	Novel
P2*	16	7	c.796 C > T; p.Gln266Ter	Compound heterozygote	Pathogenic	Novel
P3*	20	8	c.991C > T; p.Arg331Ter		Pathogenic	Kaczmarczyk et al. 2022
P4	27	6	c.721_722dupCC; p.Asp242ArgfsTer6	Compound heterozygote	Pathogenic	Novel
		7	c.796C > T; p.Gln266Ter		Pathogenic	Novel
P5	47	6	c.677C > T; p.Ala226Val	Homozygous	Pathogenic	Michaud et al. 1995
P6	54	6	c.721_722dupCC; p.Asp242ArgfsTer6	Compound heterozygote	Pathogenic	Novel
		8	c.991C > T; p.Arg331Ter		Pathogenic	Kaczmarczyk et al. 2022
P7	66	6	c.721_722dupCC; p.Asp242ArgfsTer6	Homozygous	Pathogenic	Novel

Discussion

In the present study we described the anatomical and functional characteristics of seven patients (12 eyes) with GA and performed a genetic analysis finding two novel pathogenic variants in the OAT analysis. Most of the features in the patients studied are consistent to previous reports such as age of first symptoms (second decade of life), being night blindness the most common reported symptom, also most of the phakic eyes had mild to high myopia and some degree of cataract with the need of intervention in 50% in the third decade of life (19, 22).The study by Peltola K et al made in 35 finish patients reported the mean age of diagnosis at 18 years old, in our study the mean age was 34.2 years old which can translate to a late diagnosis. Central and peripheral nervous system abnormalities (muscular weakness, cognitive and hearing impairment) have been demonstrated in patients with GA by electrophysiological studies and these findings were also presented in some patients in our study (23−24).

In the ophthalmological evaluation the mean BCVA of 0.5 logMar (Snellen 20/63) was worse than a similar case series of 7 patients with GA where a mean BCVA of 0.26 logMar was reported, this can be explained by the small number of patients studied in both series and the heterogeneity of disease severity. P2 (16 years old) was blind in one eye secondary to an untreated RRD, interestingly some cases have been reported related to this finding in pediatric patients with GA, with a novel *OAT* mutation confirmation in one case (25−26), as pediatric

RRD is uncommon even in myopic patients and GA has a very low prevalence worldwide it is important to evaluate if this complication might be another feature included in the clinical manifestations of GA.

In the fundoscopy all eyes presented patches of chorioretinal atrophy in different amounts which tended to be more coalescent in the older patients except for P1 who was 10 years old and presented an advanced stage of the disease. Another clinical finding which needs a special mention was presented in P6 (54 years old), with a well-defined area of atrophy in the macula separated from the peripheral atrophic patches by an area of preserved retina at the equator in both eyes, this is different to what has been classically described where the atrophy starts in the mid-periphery and spreads to the macula and the ora serrata in the more advanced stages (7), as we don't have previous images of this patient we can only suggest but not proof a different pattern of atrophic changes in patients with GA that also start at one point of the disease in the posterior pole and not only in the periphery. (Fig. 1). We found this pattern with similar characteristics by the fundus image of two patients presented by Sergouniotis et al. (19)

FAF findings were consistent to the atrophic area in all cases, with some degree of hyperautofluorescence in the border of the preserved retina as mentioned before (19). With the use of ultra-wide field autofluorescence, P2 and P3 (siblings) showed an interesting pattern with an evident hyperautofluorescent ring outside the arcades that separated the retina with normal autofluorescence posteriorly from the mid-periphery retina anteriorly with subtle hypoautofluorescence that did not show the same degree of autofluorescence found in the chorioretinal patches in far-periphery retina (Fig. 1). By this finding in these two patients (3 eyes), we can suggest that an initial RPE damage that is not clinically visible can precede the chorioretinal patches of atrophy which might be evidenced by the FAF. Measuring this hyper-AF ring in patients with initial damage could work as an indicator of progression and to do a more accurate follow-up.

In our study, CME was found in 50% of the eyes studied which differs from the 100% of eyes described in Sergouniotis et al. case series (19). This specific finding can be explained by a disruption of the outer blood-retinal barrier in the parafoveal area leading to a diffusion of fluid toward intraretinal spaces, maybe a lower incidence of this finding in our study could be attributed to the fact that the patients who did not present intraretinal cyst had a more preserved parafoveal area. CME in this type of retinal dystrophy has been treated with topical and oral carbonic anhydrase inhibitors, topical non-steroidal anti-inflammatory drugs, intravitreal or subtenon steroid injections, restriction of arginine in diet and vitamin B6 supplementation with widely range of response (27−28). Half of the patients presented ORT, the youngest patient (P1, 10 years old) with very advanced damage also presented this finding which demonstrates that the ORT can be considered as an indicator of the stage and marker of severity of the disease as mentioned before (29). The intraretinal hyperreflective deposits found in the ganglion cell layer had been reported previously (19), usually found near the chorioretinal atrophy, in our study found these deposits along all the preserved macula, a gliotic process due to cell death has been hypothesized in a mice model study. In our study we found more accumulation of these deposits in the patients with chronic macular edema, where they seem to coalesce and form a band-shape zone.

Interestingly, the visual field constriction found in the GP mainly in isopter I4e and the generalized decrease in sensitivity response by the topographic functional evaluation of the cones and rods response separately with scotopic and photopic perimetry in all of eyes was more severe than the clinical changes visible on fundoscopy, making these two functional objective studies parts of the follow-up evaluation of patients with GA. (Fig. 2)

Although it was not possible to make a correlation between the severity of retinal degeneration and ornithine levels as the measurements were done in a cross-sectional manner, we found a lower mean of elevated plasma ornithine levels of 586 μmol/L (excluding the patient with normal values) than reported in the finnish and japanese case series, 960 and 975 μmol/L respectively (19, 22), nevertheless the variability of the disease's severity was quite similar. The possible explanation for this finding could be related to the differences in diet between populations, but this must be properly studied. Furthermore, P5 (47 years old) with a homozygous *OAT* pathogenic variant had normal ornithine plasma levels at the time of the diagnosis, without any diet modification or treatment. Previous studies have reported patients with normal ornithine levels and clinical findings corresponding to GA but with no genetic confirmation (30–34) naming these patients "GA-like phenotype". (Fig. 3)

To date, this is the first reported case of GA confirmed by genetic testing with normal ornithine levels, supporting the theory proposed by the authors mentioned before that there might be more than one pathophysiological mechanism within the metabolic pathways of ornithine and arginine, leading to an accumulation or a decrease of substrates that eventually produce chorioretinal degeneration, this should be evaluated in more studies in the future.

Pathogenic *OAT* variants were identified in all GA patients from this cohort. Interestingly, 50% of disease-causing mutations (6/12) corresponded to the novel c.721_722dupCC (p.Asp242ArgfsTer6) variant, which was observed homozygously in two cases and in compound heterozygosity in two additional patients. While additional haplotype studies will be needed, our preliminary data supports that the c.721_722dupCC variant could be a founder OAT mutation in Mexico. A second novel *OAT* variant, corresponding to c.796C > T (p.Gln266*), was identified in a single allele in this group of patients. (Table 2)

In conclusion, the present study expands our knowledge of the clinical and genetic features of gyrate atrophy in the Mexican population. This study provides new information regarding functional and structural diagnosis to use in the future and evaluate if these tools can help us make a more accurate diagnosis on staging of the disease and a better follow-up to the patients under treatment. The most frequent mutations as well as the novel molecular findings in the Mexican population have important implications for the future genetic diagnosis of gyrate atrophy, allowing us to identify carriers of the disease and also study the genotype-phenotype correlation in larger studies in the future.

We also presented the first case with genetic confirmation of GA with normal values of ornithine that can open future lines of research to find new therapeutic alternatives. If gene therapy were to be applied in the future, we must understand the phenotypic expression so we can select the ideal patients for treatment, for example, administering the treatment to patients will less severe stages since the topographic affectation of the photoreceptors observed by means of scotopic and photopic perimetry is severely compromised in more advanced cases. Also, understanding the natural history of the disease is essential to consider whether any treatment is capable of slowing or stopping the progression of the disease.

Declarations

Acknowledgements

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the study conception and design, writing, material preparation, data collection, and analysis. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in this manuscript.

References

1. Saebo J. Atrophia Gyrata Choroideae et Retinae. British Journal of Ophthalmology. 1948;32(11):824–847. DOI: 10.1136/bjo.32.11.824.

2. Takki K. Gyrate atrophy of the choroid and retina associated with hyperornithinaemia. British Journal of Ophthalmology. 1974;58(1):3–23. DOI: 10.1136/bjo.58.1.3

3. O'Donnell JJ, Sandman RP, Martin SR. Gyrate atrophy of the retina: inborn error of L-ornithin:2-oxoacid aminotransferase. Science 1978;200:200–1. DOI: 10.1126/science.635581

4. Shen BW, Hennig M, Hohenester E, Jansonius JN, Schirmer T. Crystal structure of human recombinant ornithine aminotransferase. J Mol Biol. 1998;277(1):81–102. DOI: 10.1006/jmbi.1997.1583

5. Simell, O, Takki K. Raised plasma – ornithine and gyrate atrophy of the choroid and retina. Lancet 1973;1(7811):1031–1033. DOI: 10.1016/s0140-6736(73)90667-3

6. Rojas, S. (2012). Retina y Vítreo: Desórdenes hereditarios y distrofías de retina. (2nd edn). Manual Moderno. México.

7. Takki KK, Milton RC. The natural history of gyrate atrophy of the choroid and retina. Ophthalmology. 1981;88(4):292–301. DOI: 10.1016/s0161-6420(81)35031-3

8. Ramesh V, Benoit LA, Crawford P, Harvey PT, Shows TB, et al. The ornithine aminotransferase (OAT) locus: analysis of RFLPs in gyrate atrophy. Am J Hum Genet. 1988;42(2):365–72.

9. Krill A, Archer D. Classification of the Choroidal Atrophies. American Journal of Ophthalmology. 1971;72(3):562–585. DOI: 10.1016/0002-9394(71)90854-3

10. Vannas-Sulonen K. Progression of gyrate atrophy of the choroid and retina. A long-term follow-up by fluorescein angiography. Acta Ophthalmol (Copenh) 1987;65(1):101–109. DOI: 10.1111/j.1755-3768.1987.tb08499.x

11. Wilson DJ, Weleber RG, Green WR. Ocular clinicopathologic study of gyrate atrophy. Am J Ophthalmol 1991;111:24–33. DOI: 10.1016/s0002-9394(14)76892-8

12. Kaiser-Kupfer MI, Caruso RC, Valle D, Reed GF. Use of arginine- restricted diet to slow progression of visual loss in patients with gyrate atrophy. Arch Ophthalmol 2004;122(7):982–984. DOI: 10.1001/archopht.122.7.982

13. Santinelli R, Costagliola C, Tolone C, D'Aloia A, D'Avanzo A, et al. Low-protein diet and progression of retinal degeneration in gyrate atrophy of the choroid and retina: a twenty-six-year follow-up. J Inherit Metab Dis. 2004;27(2):187–96. DOI: 10.1023/B:BOLI.0000028779.29966.05

14. Cui X, Jauregui R, Park K, Tsang S. Multimodal characterization of a novel mutation causing vitamin B6-responsive gyrate atrophy. Ophthalmic Genetics. 2018;39(4):512–516. DOI: 10.1080/13816810.2018.1474370

15. Heller D, Weiner C, Nasie I, Anikster Y, Landau Y, et al. Reversal of cystoid macular edema in gyrate atrophy patients. Ophthalmic Genet. 2017;38(6):549–554. DOI: 10.1080/13816810.2017.1301966

16. Kim SJ, Lim DH, Kim JH, Kang SW. Gyrate atrophy of the choroid and retina diagnosed by ornithine-δ-aminotransferase gene analysis: a case report. Korean J Ophthalmol. 2013;27(5):388–91. DOI: 10.3341/kjo.2013.27.5.388

17. Zekušić M, Škaričić A, Fumić K, Rogić D, Žigman T, et al. Metabolic follow-up of a Croatian patient with gyrate atrophy and a new mutation in the OAT gene: a case report. Biochem Med (Zagreb). 2018;28(3):030801. DOI: 10.11613/BM.2018.030801

18. Elpeleg N, Korman SH. Sustained oral lysine supplementation in ornithine delta-aminotransferase deficiency. J Inherit Metab Dis. 2001;24(3):423–4. DOI: 10.1023/a:1010545811361

19. Sergouniotis PI, Davidson AE, Lenassi E, Devery SR, Moore AT, et al. Retinal structure, function, and molecular pathologic features in gyrate atrophy. Ophthalmology. 2012;119(3):596–605. DOI: 10.1016/j.ophtha.2011.09.017

20. Huang J, Fu J, Fu S, Yang L, Nie K, et al. Diagnostic value of a combination of next-generation sequencing, chorioretinal imaging and metabolic analysis: lessons from a consanguineous Chinese family with gyrate atrophy of the choroid and retina stemming from a novel OAT variant. Br J Ophthalmol. 2019;103(3):428–435. DOI: 10.1136/bjophthalmol-2018-312347

21. Katagiri S, Gekka T, Hayashi T, Ida H, Ohashi T, et al. OAT mutations and clinical features in two Japanese brothers with gyrate atrophy of the choroid and retina. Doc Ophthalmol. 2014;128(2):137–48. DOI: 10.1007/s10633-014-9426-1

22. Peltola KE, Näntö-Salonen K, Heinonen OJ, Jääskeläinen S, Heinänen K, et al. Ophthalmologic heterogeneity in subjects with gyrate atrophy of choroid and retina harboring the L402P mutation of ornithine aminotransferase. Ophthalmology. 2001;108(4):721–9. DOI: 10.1016/s0161-6420(00)00587-x

23. Valtonen M, Näntö-Salonen K, Jääskeläinen S, Heinänen K, Alanen A, et al. Central nervous system involvement in gyrate atrophy of the choroid and retina with hyperornithinaemia. J Inherit Metab Dis. 1999;22(8):855–66. DOI: 10.1023/a:1005602405349

24. Peltola KE, Jääskeläinen S, Heinonen OJ, Falck B, Näntö-Salonen K, et al. Peripheral nervous system in gyrate atrophy of the choroid and retina with hyperornithinemia. Neurology. 2002;59(5):735–40. DOI: 10.1212/wnl.59.5.735

25. Magliyah M, Alsalamah AK, AlOtaibi M, Nowilaty SR. A novel c.980C > G variant in OAT results in identifiable gyrate atrophy phenotype associated with retinal detachment in a young female. Ophthalmic Genet. 2021;42(2):204–208. DOI: 10.1080/13816810.2020.1843185

26. Barnett CP, Lam WC, Schulze A. Retinal detachment causing unilateral blindness in a 12-year-old girl with gyrate atrophy. J Inherit Metab Dis. 2009;32(5):670. DOI: 10.1007/s10545-009-1220-y

27. Çavdarlı C, Şahlı E, Çavdarlı B, Alp MN. Regression of macular edema with topical brinzolamide and nepafenac alone and identification of a novel gyrate atrophy mutation. Arq Bras Oftalmol. 2020 Mar-Apr;83(2):149–152. DOI: 10.5935/0004-2749.20200028

28. Casalino G, Pierro L, Manitto MP, Michaelides M, Bandello F. Resolution of cystoid macular edema following arginine-restricted diet and vitamin B6 supplementation in a case of gyrate atrophy. J AAPOS. 2018;22(4):321–323. DOI: 10.1016/j.jaapos.2017.12.016

29. Goldberg NR, Greenberg JP, Laud K, Tsang S, Freund KB. Outer retinal tubulation in degenerative retinal disorders. Retina. 2013;33(9):1871–6. DOI: 10.1097/IAE.0b013e318296b12f

30. Saito T, Hayasaka S, Yabata K, Omura K, Mizuno K, et al. Atypical gyrate atrophy of the choroid and retina and iminoglycinuria. Tohoku J Exp Med. 1981;135(3):331–2. DOI: 10.1620/tjem.135.331

31. Bargum R. Differential diagnosis of normoornithinaemic gyrate atrophy of the choroid and retina. Acta Ophthalmol (Copenh). 1986;64(4):369–73. DOI: 10.1111/j.1755-3768.1986.tb06937.x

32. Kellner U, Weleber RG, Kennaway NG, Fishman GA, Foerster MH. Gyrate atrophy-like phenotype with normal plasma ornithine. Retina. 1997;17(5):403–13. DOI: 10.1097/00006982-199709000-00008

33. Labiano AT, Arroyo MH. Gyrate atrophy-like phenotype with normal plasma ornithine and low plasma taurine. GMS Ophthalmol Cases. 2020;10:Doc04. DOI: 10.3205/oc000131

34. Pauleikhoff L, Weisschuh N, Lentzsch A, Spital G, Krohne TU, Agostini H, Lange CAK. Clinical characteristics of gyrate atrophy compared with a gyrate atrophy-like retinal phenotype. Eur J Ophthalmol. 2024;34(1):79–88. DOI: 10.1177/11206721231178147.
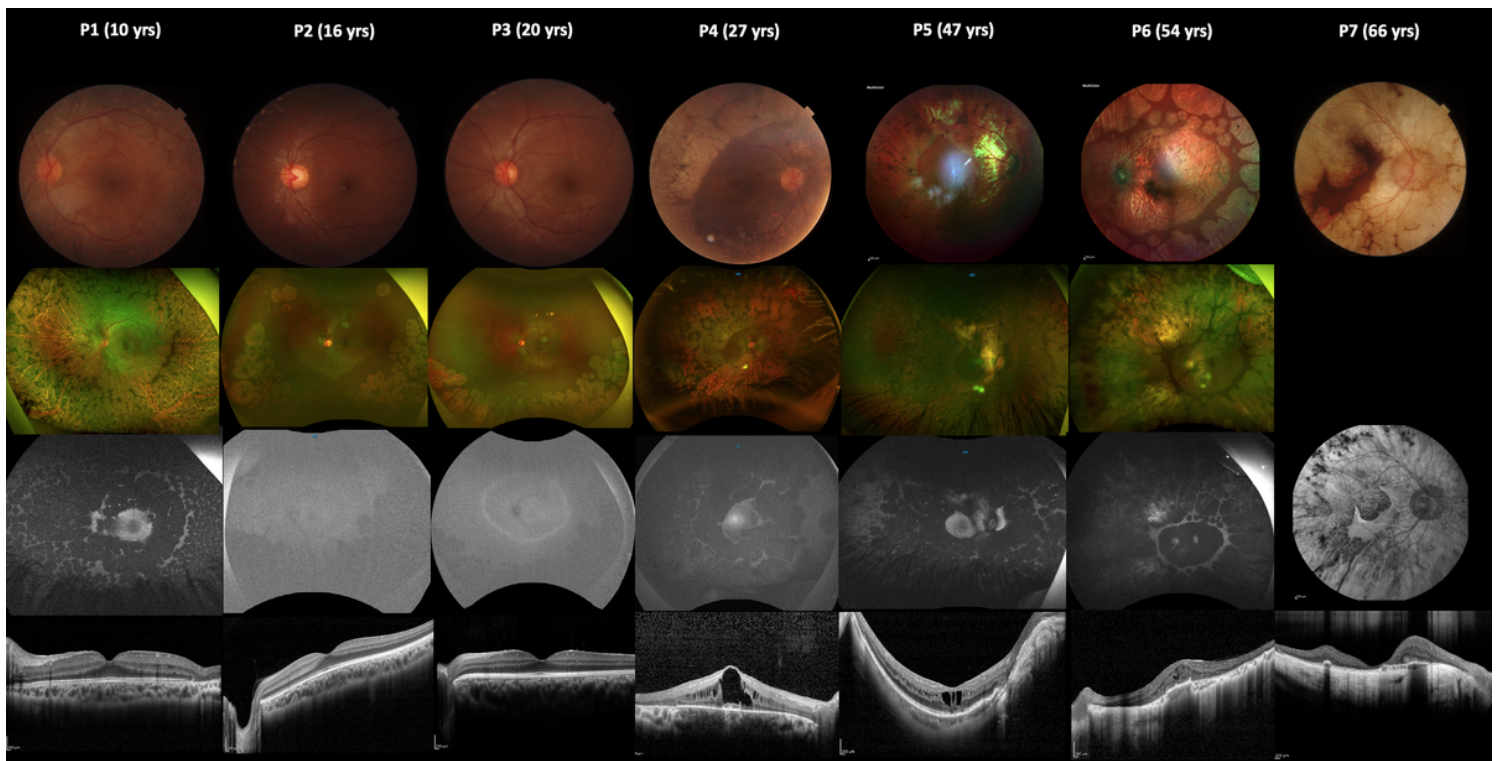
Figures

Figure 1

Structural retinal evaluation: CFC, FAF and SD-OCT of patients with GA. Each column corresponds to the case number (patients 1 through 7) and patients are numbered according to age (youngest to oldest).
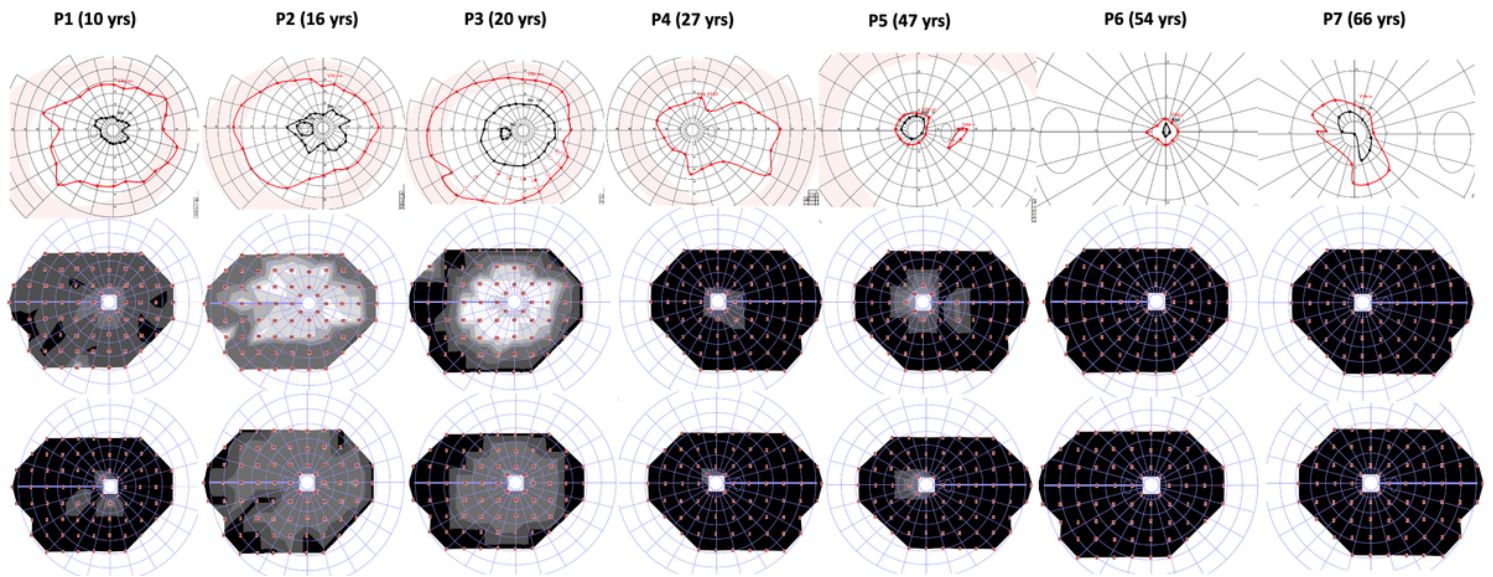

Figure 2

Functional retinal evaluation: GP and CP of patients with GA. (ffERG not shown). First CP image reports the scotopic response and second CP image reports the photopic response. Each column corresponds to the case number (patients 1 through 7) and patients are numbered according to age (youngest to oldest).
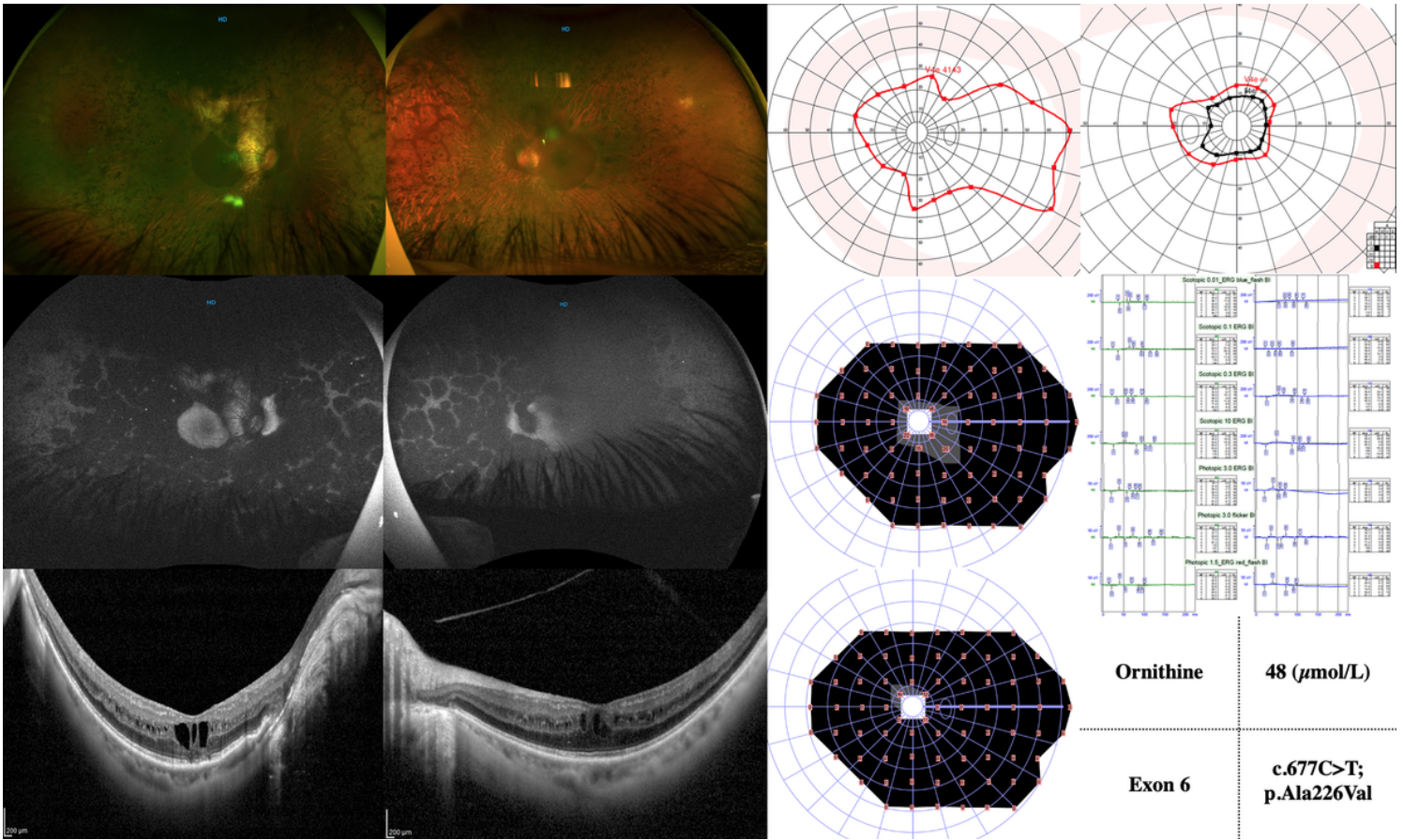
Figure 3

CFC, FAF, SD-OCT, GP, CP, ffERG, ornithine plasma levels results and *OAT* variant of patient No.5. This is the first reported case of GA confirmed by genetic testing with normal ornithine levels.