

Retinal Degeneration Associated With the G1606A Mitochondrial Mutation

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ABSTRACT: The guanine-to-adenine substitution at nucleotide 1606 (G1606A) mutation in the mitochondrial DNA transfer RNA–valine gene has been reported to cause sensorineural deafness, ataxia, myoclonus, seizures, and mental retardation. This study hereby presents a single case report of a new retinal phenotype associated with this mutation: a middle-aged woman with retinal pigment epithelium stippling, atrophy, and peripapillary (retinal pigment epithelium) dropout on fundus examination. The patient was administered an empiric trial of a mitochondrial cocktail with close monitoring of her systemic symptoms. This study identified a novel G1606A mutation to cause early-onset macular pathology resembling that previously described in the A3243G mutation.

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INTRODUCTION

Mitochondrial diseases are a clinically heterogeneous group of disorders that arise from defects in mitochondrial DNA (mtDNA).¹ The eye is one of the most commonly affected organs because of its high-energy demands, and thus, it is particularly susceptible to the consequences of mitochondrial damage.^{2,3} Common clinical features of mitochondrial diseases include ptosis, external ophthalmoplegia, optic atrophy, myopathy, cardiomyopathy, sensorineural deafness, pigmentary retinopathy, macular degeneration, and diabetes mellitus.⁴ In this report, we present a patient with early-onset macular degeneration associated with a mitochondrial guanine-to-adenine (G-to-A) substitution at nucleotide 1606 (G1606A) in the transfer RNA–valine (MT-TV) gene. The clinical and ophthalmic findings of this previously unreported association are detailed.

CASE

A 48-year-old woman presented with the diagnosis of serpiginous choroiditis noted on a routine eye examination. At that time, she did not notice any decline in her vision. She reported slow, progressive hearing loss that started in her 30s, diagnosed by an otolaryngologist as idiopathic bilateral mild-to-moderate sensorineural hearing loss, with otherwise normal ears. There was no evidence of an acoustic neuroma on brain imaging. She reported easy fatigability, poor exercise tolerance, hyperlipidemia, and sinus tachycardia. Her family history was negative for vision or hearing problems.

Her best-corrected visual acuity and intraocular pressures were 20/25 + 2 and 23 mm Hg (right) and 20/25 + 2 and 19 mm Hg (left). Pupils were equally round and reactive to light and accommodation. Extraocular movements as well as confrontational visual fields were full. The anterior segment examination was within normal limits. On fundus examination, the optic discs were pink and healthy with a cup-to-disc ratio of 0.2. In the right eye, peripapillary retinal pigment epithelium (RPE) dropout was noted, with RPE stippling in the mid periphery (**Figure 1A**). In the left eye, prominent atrophy of the RPE and choriocapillaris were noted around the optic nerve and in the temporal macula, with RPE stippling in the mid periphery (**Figure 1B**). The retinal vessels were attenuated in both eyes. Fundus autofluorescence (FAF) demonstrated peripapillary

hypo-FAF and a distinct granular mix of hyper- and hypo-FAF throughout the posterior pole (Figure 1C and D). The left eye had hypo-FAF within the macula corresponding to the RPE atrophy in this area. Spectral domain optical coherence tomography showed loss of outer retinal bands and RPE bands nasal and temporal to the fovea in both eyes (Figure 1E and F). In areas of RPE loss, the middle Sattler layer and choriocapillaris layers were diminished, and the outer choroidal vessels (Haller layer) were sparse and dilated. Electroretinogram (ERG) revealed that the amplitudes of the scotopic maximal responses were reduced by about 50% (for the -24 -dB response, 71.7 microvolts [μ V] in the right eye, 94.7 μ V in the left eye [normal range, 101 to 259 μ V]), whereas for the 0 -dB response, b-wave amplitude was 131.7 μ V in the right eye and 169.1 μ V in the left eye (normal range, 294 to 598 μ V), with a small delay in implicit times (Figure 2). The 30 -Hz flicker responses were within normal limits. Multifocal ERG showed that the pericentral wavelets were reduced in amplitudes, with an increased R1/R2 ratio of 3.85 in the right eye and 2.94 in the left eye (normal ring ratio range, 1.25 to 2.64) (Figure 2). Genetic testing was done using My Retina Tracker Program Panel Plus (version 4; Blueprint Genetics). The panel included sequence analysis and copy number variation analysis of 285 nuclear genes and 37 mitochondrial genes. Analysis of the patient's saliva sample identified a heteroplasmic (27%) MT-TV m.G1606A variant, which was deemed pathogenic. There were no other variants of interest. The patient started an empiric trial of a mitochondrial cocktail: a daily dose of 1000 mg of l-carnitine, 600 mg of coenzyme Q (CoQ), 100 mg of thiamine, 500 mg of riboflavin, 1000 mg of

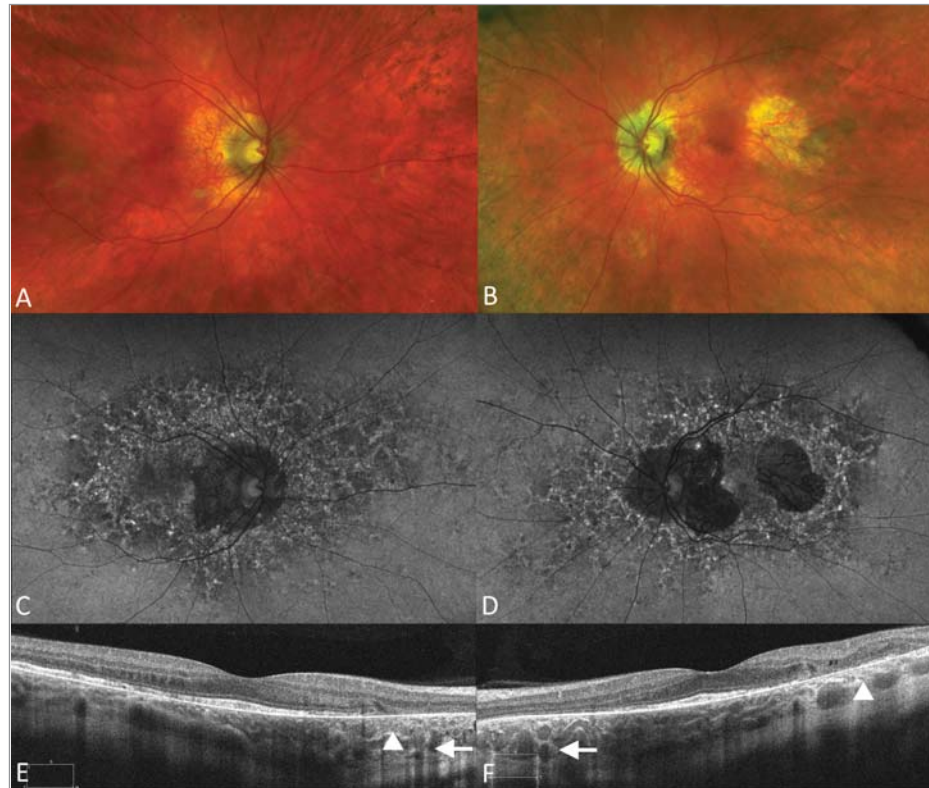


Figure 1. (A and B) Color fundus photos of right eye (A) and left eye (B). Both eyes exhibit peripapillary atrophy of the retinal pigment epithelium (RPE), mild attenuation in vessel caliber, and some mottled hyperpigmentation of the RPE in the midperipheral retina. The left eye also has atrophy of the RPE within the macula. The underlying choroidal vessels are easily visible and appear reduced in number. (C and D) Fundus autofluorescence (FAF) of the right (C) and left (D) eyes. Both eyes demonstrate peripapillary hypo-FAF and a distinct granular mix of hyper- and hypo-FAF throughout the posterior pole. The left eye has hypo-FAF within the macula corresponding to the RPE atrophy in this area. (E and F) Spectral domain optical coherence tomography of the right (E) and left (F) eyes. The arrow indicates Haller's layer, and the arrowhead points to Sattler's layer. In the right eye, there is loss of outer retinal bands and RPE bands near the optic nerve and discontinuous outer retinal bands temporal to the fovea. In the left eye, there is loss of outer retinal bands and RPE bands both nasal and temporal to the fovea. In areas of RPE loss, it is also apparent that outer choroidal vessels (Haller's layer) are sparse and dilated. The middle Sattler layer and choriocapillaris layers are diminished.

nicotinamide, 20 mg of biotin, and 10 g of l-creatine. At her 6 -month follow-up, the patient reported a subjective improvement in her exercise tolerance.

DISCUSSION

The heteroplasmic MT-TV G1606A mutation is a confirmed pathogenic point mutation causing ataxia, hearing loss, and myoclonus.⁵ It was first reported in a 48 -year-old man with ataxia, seizures, hearing loss, mild muscle weakness, mental deterioration, and cataracts.⁶ A second report of the same point mutation was described in a 37 -year-old man with ataxia, hearing loss, seizures, retinitis pigmentosa, cataracts, mental deterioration, and hypothyroidism.⁷ Genotype analysis suggested that the G1606A mutation might be related not only to changes in the DNA sequence

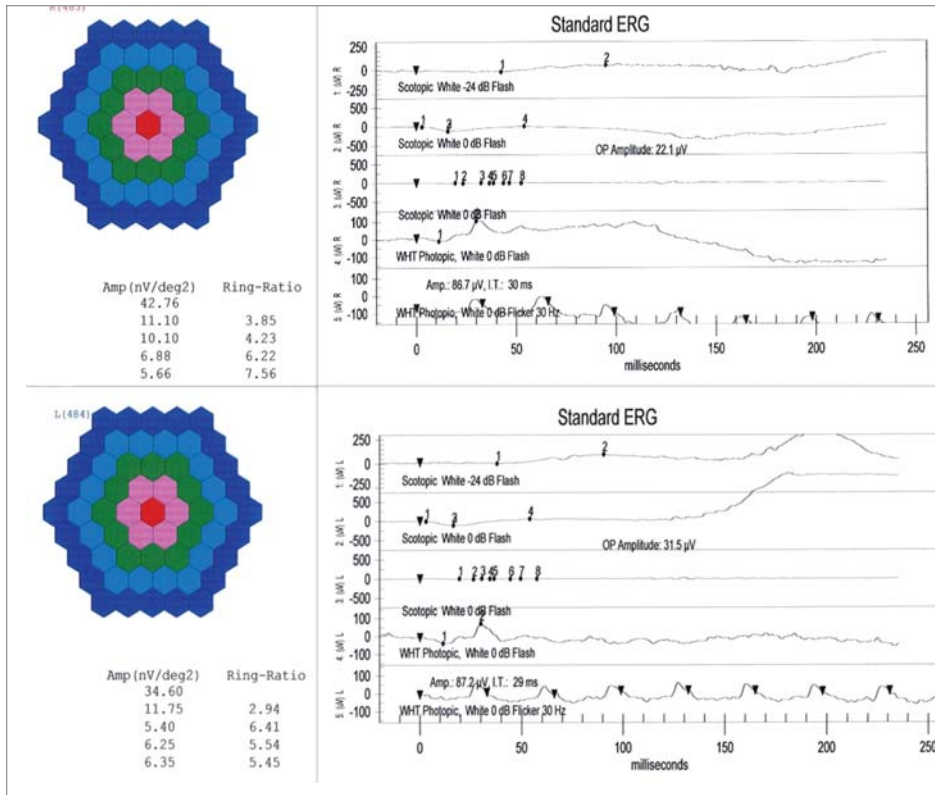


Figure 2. Multifocal ERG of right eye (top) and left eye (bottom) to the left showing that the pericentral wavelets are reduced in amplitudes, with an increased R1/R2 ratio of 3.85 in the right eye and 2.94 in the left eye (normal ring ratio range, 1.25 to 2.64). A standard ERG of right eye (top) and left eye (bottom) to the right showing around 50% reduction in the amplitudes of the scotopic maximal responses, with a small delay in the I.T. The 30-Hz flicker responses are within normal limits. ERG = electroretinogram; I.T. = implicit time; WHT = white; OP = oscillatory potentials

but also to disruptions in the secondary and tertiary structure of the MT-TV.⁸

This is the third report in the literature of the G1606A mutation, but the first one to document an associated macular degeneration. Our patient has sensorineural hearing loss, exercise intolerance, and sinus tachycardia, which may be attributed to her mitochondrial mutation. Clues for the recognition of patients with mitochondrial diseases include maternal inheritance, involvement of several organ systems, and finding of ragged-red fibers or cytochrome c oxidase-deficient fibers on muscle biopsy.⁹ In our patient, we made the diagnosis of the mitochondrial mutation after genetic testing to investigate her early macular degeneration. Although the macula had the most clinically striking involvement, the full field ERG indicated some degree of peripheral retinal involvement. This prompted a thorough systemic work-up and close monitoring of any potential neurologic symptoms that may develop in the future. The patient started a combination of nutraceuticals, a “mitochondrial cocktail,” to reduce oxidative stress.

The maculopathy described in our patient is similar to the maculopathy observed with the A-to-G substitution at position 3243 (A3243G) of the transfer RNA-leucine gene. The A3243G mutation (m.A3243G) has also been associated with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome (found in about 80% of patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes)^{10,11} and maternally inherited diabetes and deafness.^{12,13} Up to 86% of patients with A3243G-associated maternally inherited diabetes and deafness have evidence of retinal dystrophy.^{14,15} Variability of phenotypes associated with mtDNA mutations is presumed to be a consequence of heteroplasmy, the variable proportions of mutated and normal

mtDNA between individuals and also between different tissues within a single individual.¹⁶ de Laat and colleagues subdivided retinal abnormalities seen in m.A3243G into four grades: fine pigment abnormalities (grade 1); yellowish or mildly pigmented deposits (early stage of grade 2); pigments encompassing the entire macula and often encircling the optic disc (advanced grade 2); profound chorioretinal atrophy outside the fovea (grade 3); and finally, atrophy affecting the fovea with marked loss of visual acuity (grade 4).¹⁵ Our patient’s fundus is similar to that described in grade 3.

Mitochondria are involved in metabolic processes and are the main source of reactive oxygen species and an important control center for apoptosis.¹⁷ Mutations lead to defective mitochondria that may not be properly autophagocytosed; their components may undergo oxidative modification within the lysosomes, resulting in the formation of undegradable material, such as lipofuscin in RPE cells.¹⁸ The RPE is responsible for maintenance of photoreceptor function through continuous phagocytosis, recycling,

and nourishment of outer segments. Photoreceptors are constantly degraded and resynthesized, and they contain clusters of mitochondria within their inner segments.¹⁹ Whether these two cell layers are equally susceptible to the effects of the mitochondrial mutation or whether the photoreceptor damage is a consequence of the RPE disease is not known.¹⁶

The macular deposits and macular atrophy seen in our patient and in patients with m.A3243G are similar to the retinal changes seen in age-related macular degeneration (AMD). However, in AMD, drusen are located beneath the RPE on spectral domain optical coherence tomography, are less hyperautofluorescent, are more coalescent, and are located more centrally than in the m.A3243G-associated retinopathy. This differentiation is important because the atrophy in macular dystrophies may show a different rate of progression compared to atrophy in AMD.²⁰⁻²² In addition, an early recognition of syndrome-associated macular dystrophies can prompt a multidisciplinary approach involving diagnosis, prevention, and/or treatment of associated systemic diseases.²³

REFERENCES

- Smeitink J, van den Heuvel L, DiMauro S. The genetics and pathology of oxidative phosphorylation. *Nat Rev Genet* 2001;2:342-352. doi: 10.1038/35072063. PMID: 11331900.
- Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics* 2007;120:1326-1333. doi: 10.1542/peds.2007-0391. PMID: 18055683.
- Abu-Amero KK, Kondkar AA, Chalam KV. Mitochondrial aberrations and ophthalmic diseases. *J Transl Sci* 2016 3:1-11. doi: 10.15761/JTS.1000167
- Chinnery PF, Johnson MA, Wardell TM, et al. The epidemiology of pathogenic mitochondrial DNA mutations. *Ann Neurol* 2000;48:188-193. PMID: 10939569.
- Zhang S. MITOMAP: Mitochondrial DNA Base Substitution Diseases: rRNA/tRNA Mutations with Cfrn Status. Mitomap.org. 2021. Accessed February 5, 2021. Available at: <https://www.mitomap.org/foswiki/bin/view/MITOMAP/MutationsRNACfrn>.
- Tiranti V, D'Agruma L, Pareyson D, et al. A novel mutation in the mitochondrial tRNA (Val) gene associated with a complex neurological presentation. *Ann Neurol* 1998;43:98-101. doi: 10.1002/ana.410430116. PMID: 9450773.
- Sacconi S, Salviati L, Gooch C, Bonilla E, Shanske S, DiMauro S. Complex neurologic syndrome associated with the G1606A mutation of mitochondrial DNA. *Arch Neurol* 2002;59:1013-1015. doi: 10.1001/archneur.59.6.1013. PMID: 12056939.
- Schon EA, Bonilla E, DiMauro S. Mitochondrial DNA mutations and pathogenesis. *J Bioenerg Biomembr* 1997;29:131-149. doi: 10.1023/a:1022685929755. PMID: 9239539.
- Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* 2005;6:389-402. doi: 10.1038/nrg1606. PMID: 15861210; PMCID: PMC1762815.
- Goto Y, Nonaka I, Horai S. A mutation in the tRNA (Leu) (UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* 1990;348:651-653. doi: 10.1038/348651a0. PMID: 2102678.
- Kobayashi Y, Momoi MY, Tominaga K, et al. A point mutation in the mitochondrial tRNA (Leu)(UUR) gene in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). *Biochem Biophys Res Commun* 1990;173:816-822. doi: 10.1016/s0006-291x(05)80860-5. PMID: 2268345.
- van den Ouweland JM, Lemkes HH, Ruitenbeek W, et al. Mutation in mitochondrial tRNA (Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nat Genet* 1992;1:368-371. doi: 10.1038/ng0892-368. PMID: 1284550.
- de Laat P, Koene S, van den Heuvel LP, Rodenburg RJ, Janssen MC, Smeitink JA. Clinical features and heteroplasmy in blood, urine and saliva in 34 Dutch families carrying the m.3243A > G mutation. *J Inherit Metab Dis* 2012 Nov;35:1059-1069. doi: 10.1007/s10545-012-9465-2. Erratum in: *J Inherit Metab Dis* 2012;35:1155-1156. PMID: 22403016; PMCID: PMC3470685.
- Massin P, Virally-Monod M, Vialettes B, et al. Prevalence of macular pattern dystrophy in maternally inherited diabetes and deafness. GEDIAM Group. *Ophthalmology* 1999;106:1821-1827. doi: 10.1016/s0161-6420(99)90356-1. PMID: 10485557.
- de Laat P, Smeitink JAM, Janssen MCH, Keunen JEE, Boon CJF. Mitochondrial retinal dystrophy associated with the m.3243A>G mutation. *Ophthalmology* 2013;120:2684-2696. doi: 10.1016/j.ophtha.2013.05.013. PMID: 23806424.
- Daruich A, Matet A, Borruat FX. Macular dystrophy associated with the mitochondrial DNA A3243G mutation: pericentral pigment deposits or atrophy? Report of two cases and review of the literature. *BMC Ophthalmol* 2014;14:77. doi: 10.1186/1471-2415-14-77. PMID: 24906873; PMCID: PMC4059104.
- Wallace DC. Mitochondrial diseases in man and mouse. *Science* 1999;283:1482-1488. doi: 10.1126/science.283.5407.1482. PMID: 10066162.
- Bellmann C, Neveu MM, Scholl HP, et al. Localized retinal electrophysiological and fundus autofluorescence imaging abnormalities in maternally inherited diabetes and deafness. *Invest Ophthalmol Vis Sci* 2004;45:2355-2360. doi: 10.1167/iovs.03-1090. PMID: 15223817.
- Bok D. Retinal photoreceptor-pigment epithelium interactions. Friedenwald lecture. *Invest Ophthalmol Vis Sci* 1985;26:1659-1694. PMID: 2933359.
- Boon CJ, Klevering BJ, Cremers FP, et al. Central areolar choroidal dystrophy. *Ophthalmology* 2009;116:771-782, 782.e1. doi: 10.1016/j.ophtha.2008.12.019. PMID: 19243827.
- McBain VA, Townend J, Lois N. Progression of retinal pigment epithelial atrophy in stargardt disease. *Am J Ophthalmol* 2012;154:146-154. doi: 10.1016/j.ajo.2012.01.019. PMID: 22464366.
- Mauschitz MM, Fonseca S, Chang P, et al. Topography of geographic atrophy in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2012;53:4932-4939.
- Saksens NTM, Fleckenstein M, Schmitz-Valckenberg S, et al. Macular dystrophies mimicking age-related macular degeneration. *Prog Retin Eye Res* 2014;39:23-27.

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