Mitochondrial Retinopathy by MT-ATP6 Variant Revealed by Whole Genome Sequencing: A Case Report

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Running Title: MT-ATP6 associated mitochondrial retinopathy
Dear Editor,

Retinitis pigmentosa is a group of inherited retinal degeneration characterized by genetic diversity. Its manifestation includes visual loss, night blindness and loss of visual field due to the progressive loss of rod and cone photoreceptor cells. (1) The MT-ATP6 gene is a mitochondrial gene that encodes adenosine triphosphate synthase F_0 subunit 6 that is responsible for oxidative phosphorylation step, which is crucial to convert adenosine diphosphate to adenosine triphosphate. (2) Mutation in MT-ATP6 has been reported to cause Leigh’s syndrome and neurogenic weakness, ataxia, and retinitis pigmentosa syndrome (NARP). (3) Our study presents a case of mitochondrial retinopathy associated with a mutation in the MT-ATP6, initially identified in Korea through whole-genome sequencing.

This study was approved by the institutional board of Samsung Medical Center (2023-12-096) and written informed consent for publication of the case report was obtained from the patient. A 50-year-old female was referred to the retina clinic for genetic testing for retinitis pigmentosa. She presented with hand motion visual acuity in the right eye and 20/63 in the left eye with nyctalopia. She had subjective muscle weakness and fatigue. However, in the neurological examination, she exhibited normal muscle power in all joints, and there was no evidence of ataxia. She had no definitive family history of retinitis pigmentosa. Ultrawide-field fundus photography (Fig. 1A) and fundus autofluorescence (Fig. 1B) revealed atrophic retinal changes in both central and peripheral retina, along with bone spicule pigmentation in the peripheral retina. Optical coherence tomography confirmed atrophic change in the outer retina on both eyes (Fig. 1C). Her prior diagnosis of retinitis pigmentosa was established through comprehensive clinical assessments, including fundus photography, fundus autofluorescence, optical coherence tomography, and electroretinogram.

We initially conducted next-generation sequencing based gene panel sequencing focused on retinitis pigmentosa, which revealed no pathogenic variant. We performed whole-genome sequencing to identify the mutation beyond the scope of the next-generation sequencing panel. Whole-genome sequencing was performed with NovaSeq platform (Illumina, San Diego, CA, USA). Sequence reads were aligned to the Genome Reference Consortium Human Build 38 (GRCh38) with BWA-MEM (v0.7.17). Nuclear DNA analysis included variant calling with GATK HaplotypeCaller (v4.2.0) and annotation using ANNOVAR and SnpEff. For mitochondrial DNA (mtDNA) analysis, BAM file with chrM was extracted from WGS data using view option of Samtools. Mitochondrial mode of GATK Mutect2, VarDict, and mtDNA-Server were utilized for variant calling. Variants with sequencing depth ≥5X and the minor allele frequency ≥ 1% were merged and annotated with ANNOVAR, MitoMap, gnomAD and ClinVar database. Nuclear DNA achieved an average depth of 30X, while approximately
3000X coverage was obtained for mtDNA. As a result, it identified a mutation within the MT-ATP6 gene (GenBank accession no. NC_012920.1): m.8993T>C:p.(Leu156Pro), exhibiting approximately 80% heteroplasmy levels out of 4,466X sequence reads at the position.

The MT-ATP6 mutation is the most common mutation for NARP, with the m.8993T>G/C mutations being the most prevalent pathogenic variants. (4) Patients with variant typically exhibit a later onset, slower progression, and milder manifestations compared to those with the m.8993T>G variant. (3) Given the heteroplasmic nature of mitochondrial genetics, the correlation between genotype and phenotype is associated with the levels of heteroplasmy, resulting in various clinical presentation among patients. (4) A report by White et al. demonstrated that patients with m.8993T>G mutation tend to exhibit severe symptoms when heteroplasmy levels reaches 80–90%. (5) In our case, despite of a severe form of retinitis pigmentosa, other typical NARP symptoms were absent, except subjective muscle weakness. This observation may be linked to the comparatively lower heteroplasmy levels observed in the current patient. However, given that neurological manifestations can manifest later, a follow-up neurological assessment is warranted.

In conclusion, we report a Korean patient with mitochondrial retinopathy by MT-ATP6 mutation, identified through whole-genome sequencing. For patients displaying clinical features of retinitis pigmentosa without any pathogenic variants in the next-generation sequencing panel, mtDNA analysis via specific gene panels, whole-exome sequencing with mtDNA-targeted hybrid capture probes, or whole-genome sequencing with mitochondrial analysis can be helpful for uncovering pathogenic variants. As of our current knowledge, To the best of our knowledge, it is the first mitochondrial retinopathy case with a pathogenic variant in MT-ATP6 (m.8993T>C) in the Korean population.

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REFERENCES


**Figure Legend**

**Fig. 1.** Ophthalmologic features in patients with pathogenic variants in MT-ATP. (A) Ultrawide-field fundus photography showed widespread bone spicule pigimentary changes and vascular attenuation. Additionally, image blurring in the macular region of both eyes was observed due to posterior subcapsular opacity. (B) Ultrawide-field fundus autofluorescence showed diffuse and patchy hypoautofluorescence areas. (C) Optical coherence tomography of the macular region revealed atrophic changes in photoreceptor and retinal pigment epithelium layers, as well as subretinal deposits.