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Case Report

TITLE

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Introduction

Achromatopsia is an exceptionally rare early-onset retinal disorder inherited in an autosomal recessive pattern, characterized by the absence of cone photoreceptor function. This leads to a plethora of visual impairments including photophobia, nystagmus, color blindness, and markedly reduced visual acuity. The identification of the specific gene mutation in affected individuals is imperative for potential involvement in molecular genetic treatment trials. While the literature has identified causative gene mutations in five known genes (CNGA3, CNGB3, GNAT2, PDE6C, and PDE6H), a significant portion of cases remain genetically unresolved. Recently, the discovery of ATF6 as a novel gene implicated in Achromatopsia has emerged, shedding light on previously unexplained cases.

Clinical Presentation

Our case involves a 21-year-old patient who presented with a longstanding history of poor vision, photophobia, color blindness, and nystagmus. Interestingly, there was no reported history of nyctalopia, distinguishing our case from certain forms of retinal dystrophies. Past ocular history revealed a diagnosis of macular bull's maculopathy, a common clinical finding in Achromatopsia, further confirming the diagnosis. Notably, positive family history was reported, with two siblings experiencing similar visual impairments, indicating a potential genetic predisposition.

Upon examination, the patient exhibited significantly reduced visual acuity bilaterally, with the right eye measuring 0.15 and the left eye measuring 0.3. The pupils demonstrated normal size, shape, and reaction to light, ruling out afferent pupil defects. Confrontation visual fields were full to finger count, suggesting preserved peripheral vision. However, a right eye exotropia was noted for both near and distance vision, accompanied by pendular nystagmus that increased in right gaze, with a null point observed in the left gaze position.

Of particular interest was the Ishihara color vision test, which revealed a score of 1/17 plates in both eyes, consistent with the classic color blindness associated with Achromatopsia. Slit lamp examination of the anterior segment revealed no abnormalities, except for photophobia, a common complaint in patients with Achromatopsia. Funduscopic examination unveiled a clear vitreous with a normal appearing optic disc and cup-to-disc ratio of 0.3. However, macular atrophy in a bull's eye pattern, characterized by atrophic punched-out lesions with pigmented margins in both eyes. The picture was symmetrical in both eyes.

Fundus also show normal vasculature and peripheral retina, was observed bilaterally.

Cycloplegic refraction show moderate compound myopic astigmatism. Further imaging with spectral-domain optical coherence tomography (SD-OCT) revealed loss of cone inner and outer segments, interruption of the ciliary layer, and disruption of the retinal pigment epithelium (RPE) layer in the foveal area. Additionally, a shallow contour of the foveal pit was noted, consistent with foveal hypoplasia, a hallmark of Achromatopsia. Electroretinography (ERG) confirmed abnormal cone responses and a marked delay in implicit time, further corroborating the clinical diagnosis.

Genetic Analysis:

Genetic testing was performed, revealing a pathogenic variant in exon 10 of ATF6, specifically the variant c.1241_1242insA p.413Gin_414ArgPheSer (HGVS: c.1243dup, p.(Arg415Lysfs10)), in a homozygous state. This variant results in a premature stop codon, leading to either mRNA degradation (nonsense-mediated decay) or truncation of the ATF6 protein. This finding represents a significant addition to the genetic landscape of Achromatopsia and provides valuable insight into the molecular mechanisms underlying the disorder.

Comparison with Previous Reports:

Our case adds to the growing body of literature on Achromatopsia by presenting a novel variant in ATF6 associated with the disorder. Compared to previously reported cases, our patient exhibited similar clinical features including photophobia, nystagmus, color blindness, and reduced visual acuity. However, our case lacked nyctalopia, a symptom commonly observed in certain forms of retinal dystrophies, thus highlighting a distinct clinical presentation.

Notably, the identification of ATF6 as a causative gene in Achromatopsia expands our understanding of the genetic basis of the disorder. Previous studies have primarily focused on mutations in genes associated with phototransduction, such as CNGA3 and CNGB3. However, the discovery of ATF6 as a novel candidate gene underscores the complexity of Achromatopsia and the diverse molecular pathways involved in its pathogenesis.

Nucleotide Change	**Effect**	**Protein**	**Reference**
c.82+5G>T	Splicing defect	p.D28Gfs36	8
c.353delC	Truncation	p.P118Lfs31	8
c.355_356dupG	Truncation	p.E119Gfs8	9
c.797dupC	Truncation	p.N267	8
c.970C>T	Point mutation	p.R324C	8
c.1110dupA	Truncation	p.V371Sfs3	8
c.1126C>T	Truncation	p.R376	12
c.1187+5G>C	Splicing defect	p.N366Hfs12	8
c.1533+1G>C	Splicing defect	p.G512Lfs39	8
		p.L479Vfs11	
c.1691A>G	Point mutation	p.D564G	11
c.1699T>A	Point mutation	p.Y567N	8
c.909+1_1720-1del	Exon 8–14 deletion	p.I304_R573del	9
c.82+1_248-1del	Exon 2–3 deletion	p.D28_T82del	9
c.1243dup	Truncation	p.Arg415Lysfs10	our report

Table 1: Summary of identified ATF6 disease alleles

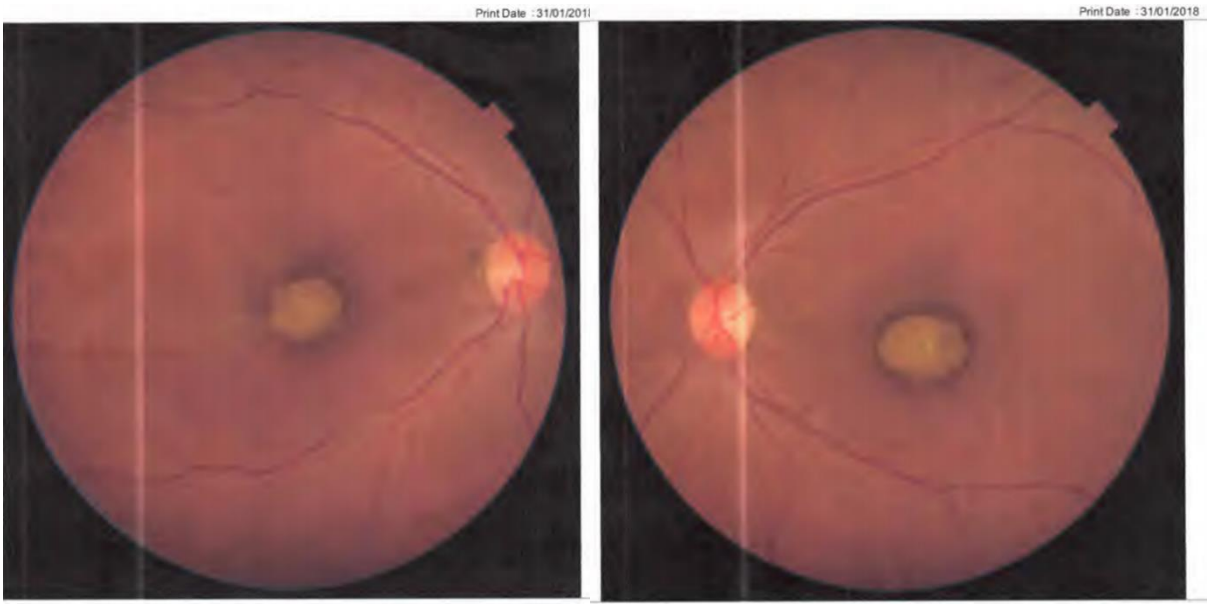
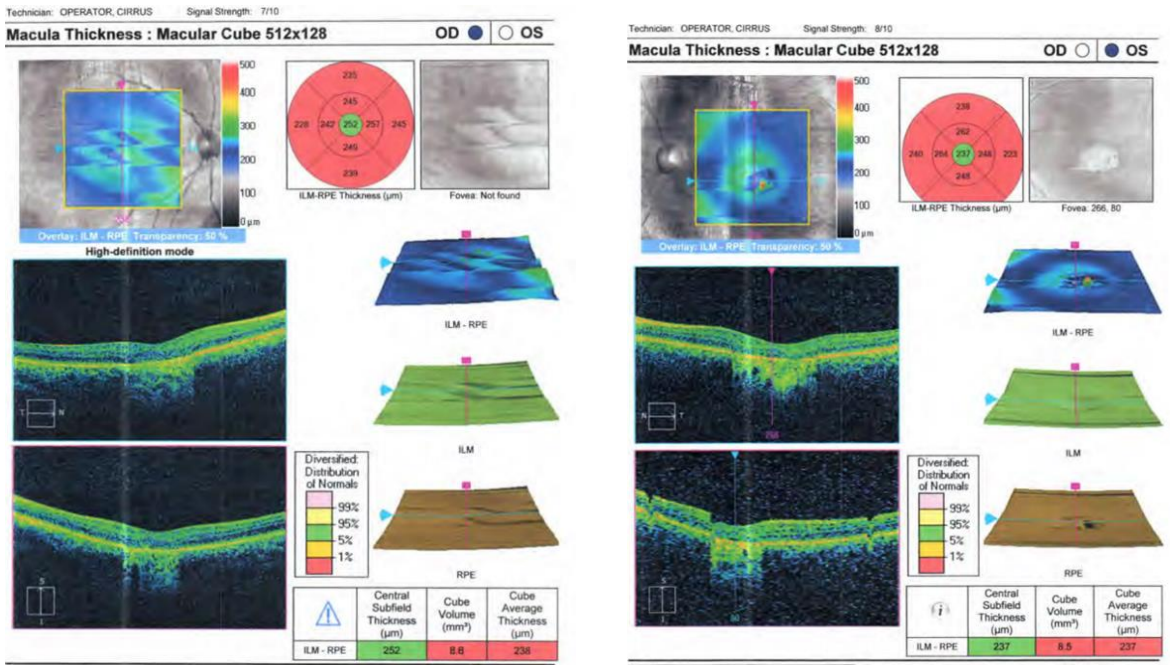


Figure 1: Clinical findings for the patient with novel pathogenic variant in exon 10 of ATF6. Fundus images of right and left eyes of the patient showed normal optic discs and severe macular atrophy (A & B).



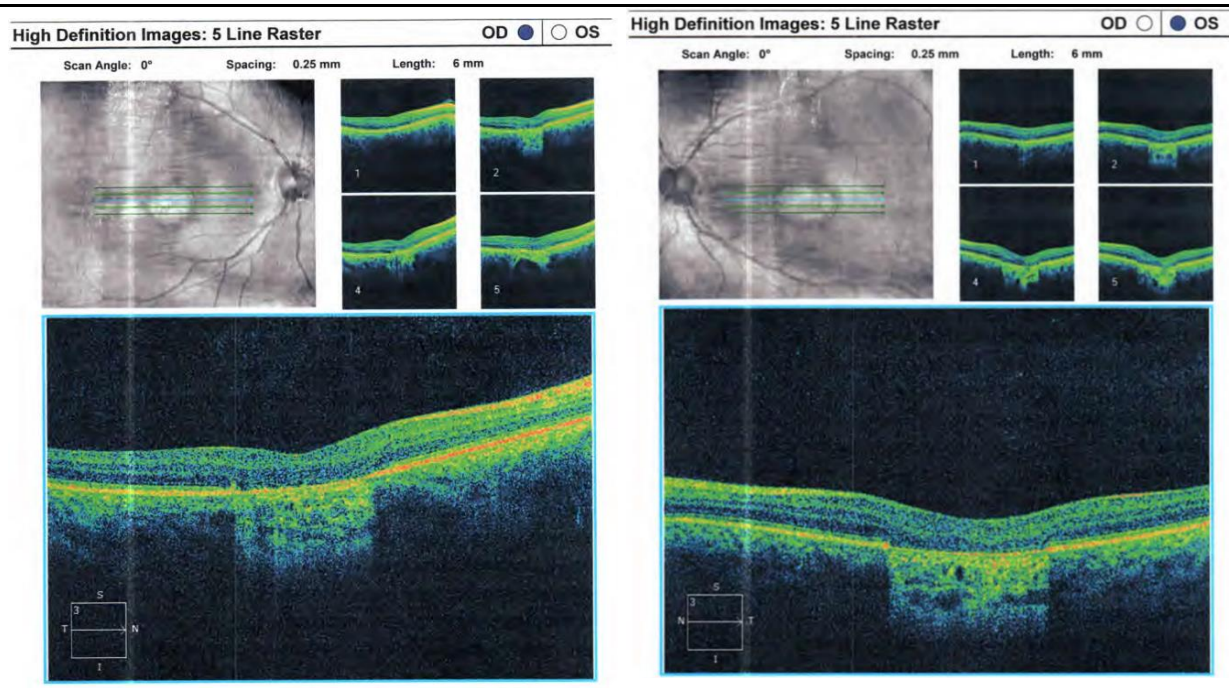


Figure 2: Spectral domain OCT images for the patient with novel pathogenic variant in exon 10 of ATF6. showed foveal atrophic patch size of optic disc in right (top) and left (bottom) eyes (A & B). The outer segments were disrupted at the fovea region (arrowheads) in both eyes (C & D).

Conclusion

In conclusion, our report highlights the clinical and genetic features of a rare case of Achromatopsia caused by a novel variant in ATF6. The identification of this variant expands our understanding of the genetic landscape of Achromatopsia and underscores the importance of genetic analysis in diagnosis and management. Further research is warranted to elucidate the molecular mechanisms underlying ATF6-associated Achromatopsia and to explore potential therapeutic interventions targeting this pathway.

Additional Report

Ahmad Al Moujahed reported two siblings from a consanguineous family of Arab descent diagnosed with ACHM. They identified a homozygous mutation in the exon 10 of the ATF6 gene c.1243dup, which leads to the introduction of a premature stop codon p.(Arg415Lysfs10) in the new coding frame. This premature stop codon is located 534 nucleotides from the last exon-exon junction and satisfies the >60-65 nucleotide

criteria for transcripts that are subject to nonsense-mediated decay (NMD). The report concluded a new homozygous single-nucleotide duplication mutation in the ATF6 gene c.1243dup in 2 patients with achromatopsia that leads to a premature stop codon. The predicted regulation of this ATF6-achromatopsia allele by NMD of the variant transcript mRNA was also demonstrated.

This comprehensive article encompasses the clinical, genetic, and additional findings related to Achromatopsia, contributing to the ongoing understanding and management of this rare retinal disorder.

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