• Letter to the Editor •

Atypical choroideremia with distinctive fundus manifestations: a case report and literature review

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Received: 2025-10-18 Accepted: 2025-11-18

DOI:10.18240/ijo.2026.06.24

Citation: Zhao MJ, Li XP, Wang R, Zeng CC, Yue ZF, Wu T. Atypical choroideremia with distinctive fundus manifestations: a case report and literature review. *Int J Ophthalmol* 2026;19(6):1209-1212

Dear Editor,

Choroideremia (OMIM: 303100) is an X-linked recessive chorioretinal dystrophy caused by pathogenic variants in the *CHM* gene. Affected males exhibit progressive bilateral retinal degeneration, typically starting with childhood-onset night blindness, followed by diffuse atrophy of the choriocapillaris and retinal pigment epithelium (RPE)[1]. Eventually, complete choroidal degeneration occurs, leading to widespread retinal dysfunction. Female carriers often present with night blindness and peripheral visual field defects.

We present a case of an adolescent male exhibiting atypical features of choroideremia, which exhibit distinct fundoscopic features. A 14-year-old boy was referred to our ophthalmology center with a two-year history of progressive night blindness and tunnel vision. Extensive eye examination at our ophthalmology center showed normal 20/20 best corrected visual acuity (BCVA) bilaterally. Findings of the anterior segment examined by slit-lamp biomicroscopy were normal bilaterally. Ultra-widefield fundus imaging identified geographic chorioretinal atrophy, yet did not involve the macular area of both eyes (Figure 1). Notably, the central 5° of the posterior pole maintained preserved choroidal architecture integrity. Fundus autofluorescence (FAF) imaging revealed gyrate areas of reduced signal in the mid-peripheral retina, along with plaque-like lesions formed by the confluence of multiple foci areas, while a central island of preserved autofluorescence was observed adjacent to the macula within the posterior pole (Figure 1). Optical coherence tomography (OCT) revealed preserved choroidal thickness in the foveal region, with clearly defined anatomical boundaries of the RPE-Bruch's membrane complex and intact ellipsoid/interdigitation zones. However, the peripheral retina demonstrated irregular atrophy characterized by thinning of choroids, irregular atrophy of RPE-Bruch's complex and irregular disruption of photoreceptor layer morphology (Figure 1).

Whole-exome sequencing identified a novel frameshift mutation (c.1725_1729delCTCTG) in the *CHM* gene, which is predicted to cause a truncated protein (p.Cys575Trpfs*9). No other significant pathogenic variants were detected. This frameshift mutation, which is not present in population genomic databases (gnomAD and 1000 Genomes Project), exhibits functional concordance with the characteristic pathophysiology of choroideremia. The patient's family members (father, mother, and sister) underwent comprehensive standardized ophthalmic evaluations at our institution. All family members demonstrated BCVA of 20/20 with unremarkable ocular finding. Sanger sequencing revealed heterozygous *CHM* variants (c.1725_1729delCTCTG) in both the mother and sister, thereby confirming their carrier status for the X-linked choroideremia-associated mutation (Figure 2). This study received ethical approval from Hainan Hospital of Chinese PLA General Hospital. All patients provided written informed consent, which specifically authorized the use of their clinical data and case images for publication. We explained the etiology and pathogenesis to the child's parents and advised

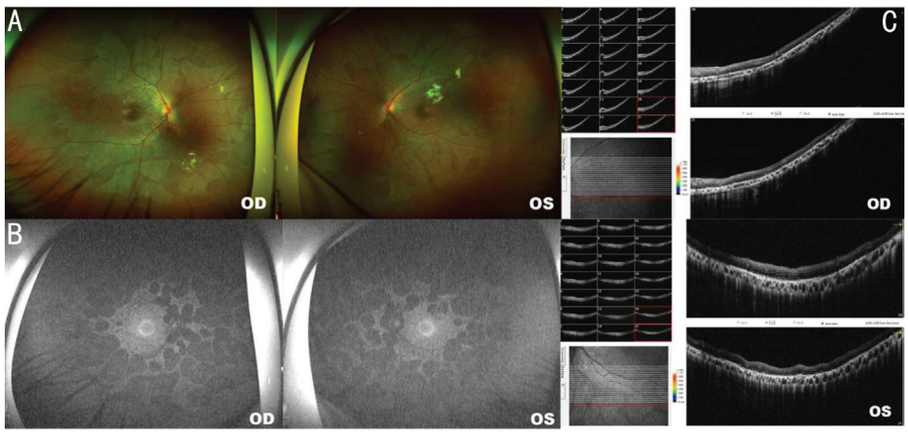

Figure 1 A 14-year-old boy exhibiting atypical features of choroideremia A: The ultra-widefield fundus photography of the patient identified severe scalloped chorioretinal atrophy and preserved macular area; B: The autofluorescence imaging examination of the patient's fundus revealed gyrate areas of hypoautofluorescence in the mid-peripheral retina, along with a preserved autofluorescence central island; C: OCT images of the patient's fundus revealed preserved choroidal thickness in the foveal region, with clearly defined anatomical boundaries of the RPE-Bruch's membrane complex and intact ellipsoid/interdigitation zones. OCT: Optical coherence tomography; RPE: Retinal pigment epithelium.

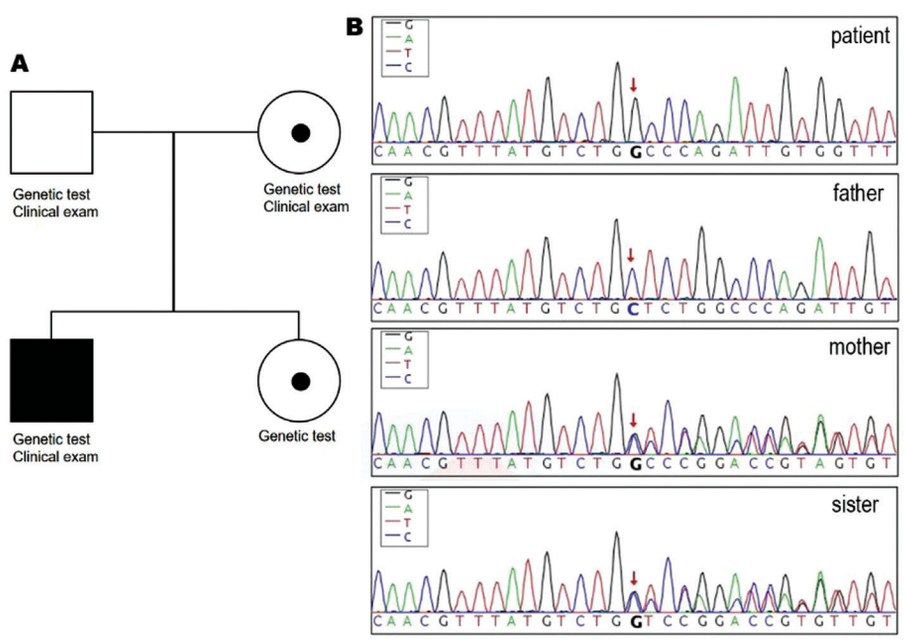

Figure 2 Whole-exome sequencing identified a novel frameshift mutation (c.1725_1729delCTCTG) in the *CHM* gene A: Pedigree showing the proband's family history. His sister and mother showed typical carrier phenotype of choroideremia on clinical examination. They both have genetically confirmed choroideremia carrier status. The father had normal ocular examination. B: Comparison of Sanger sequencing traces for proband's father, mother, sister, and our patient.

biannual monitoring of visual acuity and visual fields. To date, the child's vision and visual fields have shown no significant changes.

DISCUSSION

Choroideremia, a hereditary ocular disorder, has been the subject of extensive investigation since its initial description in 1872 and the subsequent cloning of the *CHM* gene in the 1990s. The disease is caused by mutations in the *CHM* gene, which is located on Xq21.2 and encodes Rab escort protein 1 (REP-1), a protein that plays a critical role in Rab GTPase prenylation. REP-1 interacts with fresh Rab proteins and transports them to an Rab geranylgeranyl transferase (RGGT) in order to form the functional complex, facilitating lipid modification of Rab GTPases, which is crucial for membrane targeting[2]. Loss of function of REP-1 impairs the prenylation of proteins essential for vesicular traffic and fusion of internalized organelles. In turn these failures eventually lead to a progressive attrition of photoreceptors, RPE and choroidal vasculature by stalling intracellular protein traffic and exchange of nutrients that is essential to metabolism of

RPE and photoreceptors that rely on healthy Rab proteins.

Choroideremia typically manifests in childhood with initial night blindness. The disease progresses from peripheral visual field constriction to concentric loss (tunnel vision), culminating in end-stage blindness. A gradual decline in central vision occurs, significantly worsening in patients' 50s and 60s due to macular involvement. A high percentage of patients exhibit color vision deficiencies, primarily red/green deficits, consistent with photoreceptor dysfunction[3].

Early fundoscopy reveals peripheral RPE hyperpigmentation, progressing to extensive chorioretinal atrophy with scleral exposure and choroidal vessel visibility. OCT shows an initial RPE layer thinning and disorganized photoreceptor outer segments in the early stages that eventually evolves with nearly complete atrophy of the RPE-choroid with atrophic macular islands[3]. FAF revealing well-demarcated hyperfluorescent macular islands in early to mid-stage cases among males and diffuse hypofluorescence in advanced stages of the disease. This presentation is inconsistent with the classic ocular fundus phenotype of choroideremia and has not been previously reported in atypical cases. Atypical choroideremia is typically associated with early macular atrophy, cystoid macular edema, posterior subcapsular cataract, and choroidal neovascularization, while the fundus findings align with the above description[4]. Our patient presented with bilateral and symmetrical scalloped areas of peripheral chorioretinal atrophy in the early stage, within which large choroidal vessels were clearly visible—a appearance highly reminiscent of gyrate atrophy (GA) of the choroid and retina. GA is an autosomal recessive disorder caused by mutations in the ornithine aminotransferase (OAT) gene, leading to OAT deficiency. This results in hyperornithinemia, which is toxic to RPE, causing progressive chorioretinal atrophy. Its clinical manifestations share similarities with choroideremia, including night blindness and progressive visual field defects. However, GA is frequently associated with high myopia and early-onset posterior subcapsular cataracts, which serve as distinguishing features[5]. This observation suggests that although choroideremia and GA are fundamentally distinct in their genetic and biochemical bases, they may share common downstream pathways or convergent cellular stress responses at certain stages of disease progression. Although the initiating factors of GA and choroideremia differ, oxidative stress and energy metabolism dysfunction may represent key convergent mechanisms. In GA, ornithine accumulation disrupts amino acid metabolism, depletes cellular phosphocreatine, and compromises the energy buffer system, rendering retinal cells more vulnerable to metabolic stress. Elevated ornithine also induces mitochondrial dysfunction, promoting excessive reactive oxygen species (ROS) generation and widespread oxidative damage[6]. In choroideremia, deficiency of REP-1 impairs intracellular protein trafficking and degradation, similarly leading to mitochondrial dysfunction and ROS accumulation[7]. Besides, dysfunction and death of RPE cells are central to both diseases. In GA, high ornithine and its metabolites directly damage RPE tight junctions and polarity, impairing key functions and initiating focal RPE atrophy, followed by secondary degeneration of the choriocapillaris and photoreceptors. The gyrate pattern of chorioretinal atrophy may arise from regional variations in RPE metabolic activity or differential susceptibility to stressors[6]. If REP-1 deficiency causes non-uniform RPE dysfunction, localized cell death and subsequent coalescing atrophy could form a gyrate-like pattern. Thus, distinct etiologies may induce highly similar atrophic morphology *via* oxidative stress and disrupted RPE homeostasis, offering new insights for differential diagnosis.

Although the patient's fundus presentation bore a close resemblance to GA, a definitive diagnosis of choroideremia was established based on genetic sequencing that revealed a mutation in the *CHM* gene without a concomitant mutation in the *OAT* gene. This diagnosis was further supported by the absence of bone spicule pigmentation, optic disc pallor, and posterior pole cholesterol crystal deposits. Additionally, the patient did not exhibit progressive external ophthalmoplegia, cerebellar ataxia, psychiatric history, or a history of high-dose medication intake, effectively excluding differential diagnoses such as retinitis pigmentosa, Kearns-Sayre syndrome, Bietti crystalline dystrophy, and thioridazine hydrochloride retinal toxicity[2]. This case underscores the critical role of genetic sequencing in achieving a precise diagnosis.

Due to its monogenic recessive nature and slow progression, choroideremia offers an extended therapeutic window, making it ideal for gene therapy. Although subretinal AAV2-REP1 (timrepigene emparvovec) delivery has been tested in clinical trials, translational challenges in animal models delayed human trials until 2012[8]. Initial Phase I/II trials (*e.g.*, NCT01461213) demonstrated acceptable safety and variable visual outcomes: patients with lower baseline acuity (≤65 ETDRS letters) showed improvements up to +21 letters, whereas those with better vision (≥73 letters) exhibited minimal response. Subsequent multinational trials (NCT02077361, NCT02671539, NCT02553135) confirmed therapeutic potential in advanced disease. Later studies, including the REGENERATE trial, focused on earlier-stage patients but found no significant difference in BCVA change over 24mo, likely due to slow disease progression[9]. Recent Phase III results (NCT02489180) did not meet primary efficacy endpoints but highlighted that younger patients with higher baseline acuity and preserved retinal integrity were more likely to benefit[10]. Early identification and diagnosis of

choroideremia are critical, as they enable patients to undergo gene replacement therapy before severe visual impairment occurs, thereby optimizing long-term visual outcomes. Our findings expand the disease's genotypic and phenotypic spectrum and underscore the importance of molecular diagnosis in informing clinical management. Furthermore, identifying pathogenic variants provides a foundation for patients and families to participate in future targeted gene therapy trials, highlighting significant clinical and scientific relevance.

ACKNOWLEDGEMENTS

Data Availability Statement: All data relevant to the study are included in the article.

Foundation: Supported by Hainan Natural Science Foundation General Project (No.823MS163).

Conflicts of Interest: Zhao MJ, None; **Li XP,** None; **Wang R,** None; **Zeng CC,** None; **Yue ZF,** None; **Wu T,** None.

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