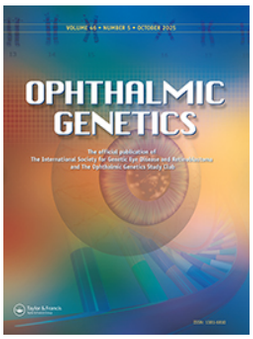

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CASE REPORT

A new genotype of the *IDH3A* gene causes retinitis pigmentosa, generating functional dyschromatopsia from early childhood

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ABSTRACT

Introduction: We report the case of a 42-year-old Venezuelan woman with childhood-onset autosomal recessive retinitis pigmentosa type 90 (RP90), presenting an unusual and distinctive clinical phenotype characterized by macular pseudocoloboma, very early-onset acquired color vision disorder progressing to severe functional dyschromatopsia, and early-onset severe posterior subcapsular cataracts. Her affected brother exhibited a similar phenotype, while her parents and the other two siblings remained unaffected.

Methods and Results: Massive parallel sequencing identified two novel *IDH3A* variants: c.127G>T (chr15:78449926 G>T; no dbSNP entry) and c.419T>C (chr15:78454052T>C; no dbSNP entry), in compound heterozygosity and confirmed to be in *trans* location. Both missense variants, absent from population databases, were predicted to be deleterious by multiple *in silico* tools and are located in critical domains involved in enzymatic complex stability, catalytic activity and subunit interactions.

Conclusions: This case reinforces the association between *IDH3A* mutations and *RP90*, corroborates key phenotypic features described in limited published reports—the presence of macular pseudocoloboma—and expands the mutational spectrum of the gene. Moreover, it highlights the role of mitochondrial metabolism in photoreceptor degeneration and proposes a link between them. Our findings underscore the need for functional studies to elucidate the pathogenic mechanisms underlying *IDH3A*-related retinopathies.

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KEYWORDS
IDH3A; retinitis pigmentosa; compound heterozygous; pseudocoloboma; functional dyschromatopsia

1. Introduction

Retinitis Pigmentosa (RP; OMIM#268000) represents the most common form of inherited retinal dystrophy (IRD), with a global prevalence of approximately 1 in 4000 individuals (1). The core phenotypic features are comprehensively cataloged in the Human Phenotype Ontology (HPO) database (accessed 29 April 2025; https://hpo.jax.org/browse/gene/NCBIGene:3419). This heterogeneous group of disorders is hallmarked by the progressive degeneration of photoreceptors, initially involving rod cells—responsible for scotopic vision—leading to early symptoms such as nyctalopia and peripheral visual field constriction. As the disease advances, cone photoreceptors—essential for photopic vision—also degenerate, culminating in loss of central visual acuity. In the end stages, RP typically results in widespread retinal atrophy and irreversible blindness (2, 3).

In typical cases of RP, fundoscopic examination reveals hallmark features including optic disc pallor, attenuation of the retinal vasculature, mottling of the retinal pigment epithelium (RPE), and characteristic peripheral bone-spicule pigmentation. Additionally, approximately 50% of affected individuals develop posterior subcapsular cataracts, which are readily detectable via slit-lamp biomicroscopy (3).

RP exhibits remarkable heterogeneity at the genetic, phenotypic, and inheritance pattern levels. To date, over 80 disease-associated genes have been identified, and—together with epigenetic modifiers—they contribute to the extensive clinical variability that often hinders accurate diagnosis and precise characterization (RetNet, April 2025) (4).

Among the rarest genetic determinants, the *IDH3A* gene was firstly implicated in autosomal recessive RP by Pierrache *et al.* in 2018. *IDH3A* gene encodes the catalytic subunit alpha of the mitochondrial NAD^+ 3-dependent isocitrate dehydrogenase, a key enzyme in the tricarboxylic acid (TCA) cycle (5). Due to its extremely low allele frequency, it remains scarcely documented in the literature.

In this work, we present the case of two siblings with RP associated with the compound heterozygous causative genotype in the minor gene *IDH3A*, highlighting a rare and distinctive RP phenotype. Their identification also underscores the importance of including low-frequency causative genes in

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rigorous sequencing analyses for patients with inherited retinal dystrophies.

2. Methods

2.1. Genetic analysis

Genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. Library preparation was carried out with the Comprehensive Exome Panel (Twist Bioscience, San Francisco, CA, USA), and sequencing was performed on the NovaSeq 6000 System (Illumina, San Francisco, CA, USA). The analysis targeted 111 genes associated with retinitis pigmentosa (EXN1013_V3), focusing on variants located within exonic regions or canonical splice sites (including at least 5 bp of flanking intronic sequence). Only variants with a variant allele frequency (VAF) greater than 30% were considered for downstream analysis.

Structural and crystallographic modeling data regarding *IDH3A* protein were available in the Uniprot database, which can be consulted at the link: https://www.uniprot.org/uniprotkb/P50213/entry#structure (Last accessed 05/08/2025).

2.2. Clinical examination

The patient underwent a comprehensive ophthalmological evaluation, including best-corrected visual acuity (BCVA) assessment using a Topcon ACP-8 automatic optotype projector (Topcon Corporation, Tokyo, Japan) positioned 5 meters from the subject under standardized photopic conditions. Objective refraction was performed with the Topcon KR-8800 autorefractor-keratometer, and intraocular pressure (IOP) was measured using the Topcon CT-80 non-contact tonometer. Anterior segment examination was conducted using the Topcon SL-D4 slit lamp system. Fundus imaging was performed with the CLARUS™ 500 fundus camera (Carl Zeiss Meditec, Germany), while macular morphology was evaluated by optical coherence tomography (OCT; SPECTRALIS OCT+HRA, Heidelberg Engineering, Heidelberg, Germany). Visual field testing employed the Humphrey® Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA), using the Swedish Interactive Threshold Algorithm (SITA) Standard strategy with the 24–2 protocol.

3. Results

We conducted a diagnostic workup and genetic counseling for a 42-year-old woman with a clinical diagnosis of slowly progressive RP since the age of 6, in the absence of prior genetic testing. Her initial manifestations included very early-onset or even congenital color vision deficiency (HP:0000551), bilateral high-grade posterior subcapsular cataracts (HP:0007787) requiring surgical removal at age 45, and nyctalopia (HP:0000662). The color vision impairment progressed to complete functional achromatopsia.

The patient exhibited clinical features consistent with RP, including optic disc pallor, severe attenuation of retinal arterioles, peripheral bone spicule pigmentation, and progressive visual field constriction. Notably, a prominent macular pseudocoloboma was observed, representing the most noteworthy feature of the retinal phenotype. Fundus autofluorescence revealed central hypoautofluorescence surrounded by a ring of increased signal, consistent with macular atrophy.

The patient descends from four grandparents of Venezuelan origin and has three siblings, two unaffected who were unavailable for evaluation and one brother with a similar clinical phenotype. Both parents underwent cataract surgery later in life, at ages 65 and 70, respectively. A comprehensive phenotypic profile, annotated using HPO terms, is provided in Table 1. Results of detailed ophthalmologic testing are shown in Figure 1.

Massive parallel sequencing revealed that the patient is a compound heterozygote for two previously unreported variants in the *IDH3A* gene (NM_005530.3), both absent from population databases (gnomAD v4.1) and not documented in the scientific literature: c.127 G>T, chr15:78157584 G>T, p.(Gly43Cys), and c.419T>C, chr15:78161710T>C, p.(Val140Ala), neither of which has a dbSNP entry. According to American College of Medical Genetics and Genomics (ACMG) criteria, PP4 (family genotype/phenotype segregation was highly specific for the disease with a IDH3A genetic etiology), PM3 (detected in trans for compound heterozygous state in both affected siblings), PM2, PP3 were applicable, based also on *in silico* pathogenicity predictions for both variants.

Familial segregation analysis of the variants showed that the other affected sibling carried the same pathogenic variant combination, and the mother was a heterozygous carrier of only p.(Gly43Cys). Therefore, segregation analysis confirmed the variants were arranged *in trans*.

4. Discussion

The *IDH3A* gene (OMIM *601149) has been associated with retinitis pigmentosa type 90 (RP90; OMIM#619007), a rare autosomal recessive disorder. Cases of RP90 have been described both with and without macular pseudocoloboma (5–7).

In this family, we identified a novel pathogenic genotype in *IDH3A*, consisting of two previously unreported variants located *in trans*. Although both variants are still formally classified as variants of uncertain significance (VUS) based on current ACMG criteria, multiple lines of evidence—including *in silico* predictions, conservation metrics and familial segregation, supported their likely pathogenicity: PP4, PM3, PM2, PP3. The strong genotype—phenotype correlation observed in the two affected siblings reinforces the causal role of the compound heterozygous genotype p.(Gly43Cys)/p.(Val140Ala).

Structural modeling and crystallographic data (8, 9) indicated that the p.(Gly43Cys) variant is located at the terminal position of an α-helix within the large domain of the *IDH3A* protein, adjacent to the NAD^+ binding site. Positional information for codon p.43Gly of the IDH3A protein (GENCODE: ENST00000299518.2, RefSeq: NM_005530.2, UniProt: P50213), cDNA: c.127–129 GGC provides a change tolerance score (dn/ds) of 1.31, which was classified as tolerant. This

Table 1. HPO terms associated with *IDH3A* gene mutations and clinical manifestations in the current patients.

HPO	HPO Terms	1. Index case	2. Affected Sibling
HP:0030488	Abnormal central response of multifocal electroretinogram	YES	YES
HP:0000512	Abnormal electroretinogram	YES	YES
HP:0030466	Abnormal full-field electroretinogram	YES	YES
HP:0008046	Abnormal retinal vascular morphology	YES	YES
HP:0007703	Abnormality of retinal pigmentation	YES	YES
HP:0007843	Attenuation of retinal blood vessels	YES	YES
HP:0000007	Autosomal recessive inheritance	YES	YES
HP:0000618	Blindness	YES	YES
HP:0007737	Bone spicule pigmentation of the retina	YES	YES
HP:0011463	Childhood onset	YES	YES
HP:0000551	Color vision defect	YES	YES
HP:0000405	Conductive hearing impairment	NO	NO
HP:0001133	Constriction of peripheral visual field	YES	YES
HP:0011505	Cystoid macular edema	NO	NO
HP:0000501	Glaucoma	NO	NO
HP:0025158	Hyperautofluorescent retinal lesion	NO	NO
HP:0000842	Hyperinsulinemia	NO	NO
HP:0000563	Keratoconus	NO	NO
HP:0000662	Nyctalopia	YES	YES
HP:0000639	Nystagmus	NO	NO
HP:0000602	Ophthalmoplegia	NO	NO
HP:0000648	Optic atrophy	NO	NO
HP:0012426	Optic disc drusen	NO	NO
HP:0000543	Optic disc pallor	YES	YES
HP:0007994	Peripheral visual field loss	YES	YES
HP:0000613	Photophobia	NO	NO
HP:0030786	Photopsia	NO	NO
HP:0030610	Photoreceptor outer segment loss on macular OCT	YES	YES
HP:0007787	Posterior subcapsular cataract	YES	YES
HP:0007675	Progressive night blindness	YES	YES
HP:0007663	Reduced visual acuity	YES	YES
HP:0001105	Retinal atrophy	YES	YES
HP:0000546	Retinal degeneration	YES	YES
HP:0007722	Retinal pigment epithelial atrophy	YES	YES
HP:0000407	Sensorineural hearing impairment	NO	NO
HP:0000486	Strabismus	NO	NO
HP:0000505	Visual impairment	YES	YES
Clinical Characteristics			
Refractive error, spherical equivalent (age)		RE −2.54 D; LE + 1.50 D	RE + 1.50 D; LE + 1.75D
Snellen visual acuity (age)		RE 20/400; LE 20/400 (43)	RE 20/400; LE 20/200 (48)
Intraocular pressure (mmHg)		RE 13; LE 13	RE 14; LE 13
Fundus (age)		Optic disc pallor, attenuation of the retinal arterioles, marked macular pigmentary changes with coloboma-like central atrophy, and dense bone spicule pigmentation in the mid-periphery (43)	Optic disc pallor, attenuation of the retinal arterioles, marked macular pigmentary changes with coloboma-like central atrophy, and dense bone spicule pigmentation in the mid-periphery (48)
Fundus autofluorescence (age)		Marked macular hypoautofluorescence surrounded by a broad ring of increased signal, gradually fading toward the periphery (43)	Marked macular hypoautofluorescence surrounded by a broad ring of increased signal, gradually fading toward the periphery (48)
Automated Perimetry—Visual Field Index (age)		0% (43)	0% (48)
Onset age		6	5

Abbreviations: D: diopters; HPO: Human Phenotype Ontology; LE: left eye; RE: right eye.

residue lies within the conserved protein domain PF00180, and no pathogenic single nucleotide variants (SNVs) at this position have been previously reported in ClinVar. However, the replacement of glycine (a highly flexible residue) by cysteine in a structurally constrained α-helix may induce conformational distortion, destabilizing the catalytic domain or interfering with proper NAD^+ binding. This could impair enzymatic activity of mitochondrial isocitrate dehydrogenase, disrupting the TCA cycle and leading to chronic energy imbalance and oxidative stress in photoreceptor cells, thereby contributing to their progressive degeneration and the observed retinal phenotype.

In contrast, the p.(Val140Ala) variant is located within a β-sheet at the αβ/αγ heterodimer interface (8–10), a region critical for allosteric regulation and subunit assembly. Despite the biochemically conservative from Val to Ala substitution,

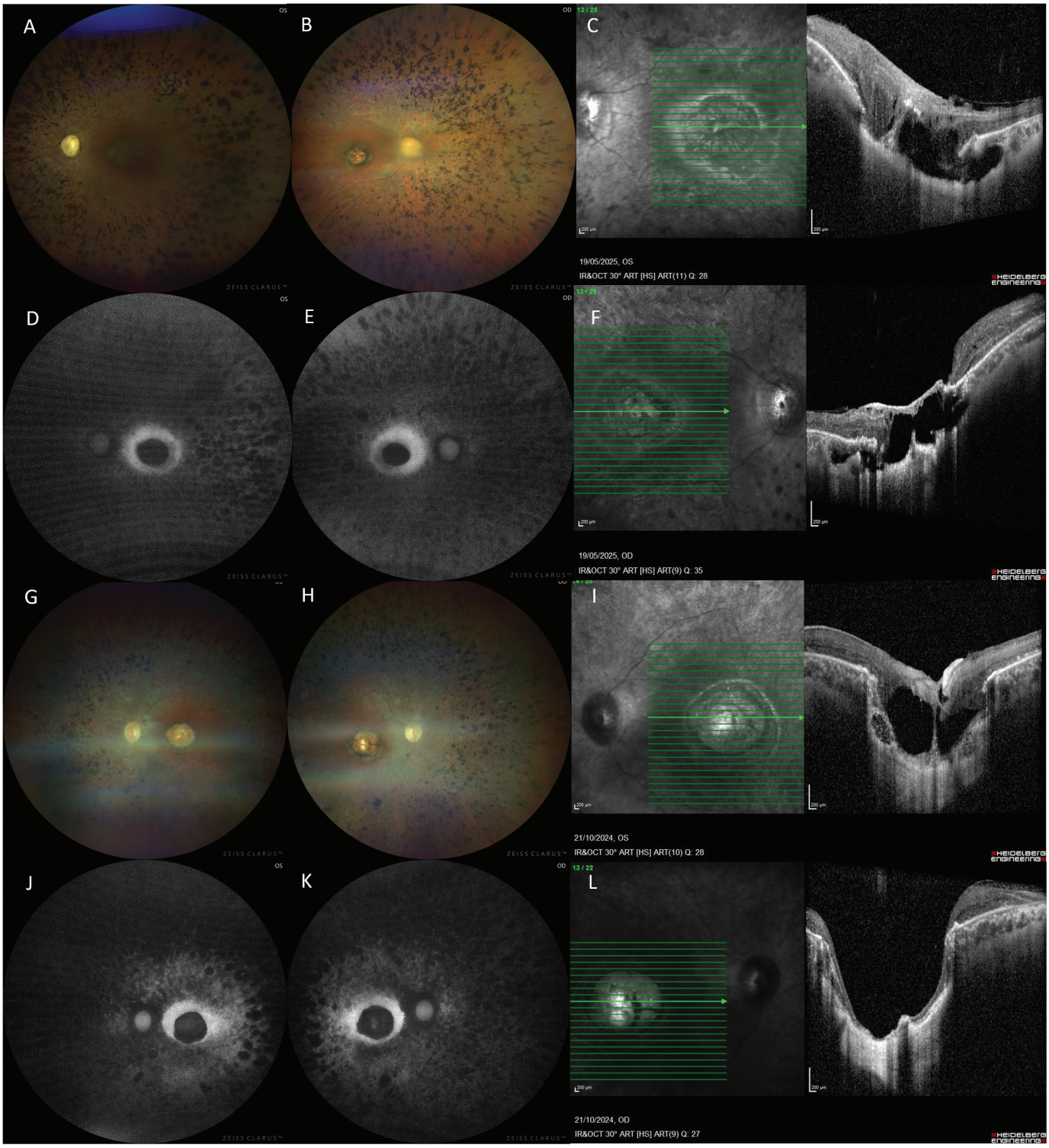

Figure 1. Color fundus photographs, fundus autofluorescence (FAF) and optical coherence tomography (OCT) of Patient 1 (A–F) and Patient 2 (G–L). (A–B, G–H) Bilateral waxy-pale optic discs, severe attenuation of retinal vessels with silver-wiring of arterioles, midperipheral bone-spicule pigmentation and macular pseudocoloboma-like lesions. (C, F, I, L) OCT revealed a sharply demarcated macular excavation involving all retinal layers, with loss of the outer retina, retinal pigment epithelium, and choriocapillaris. The foveal contour was disrupted, and the lesion extended to the scleral level, consistent with a pseudocoloboma-like configuration. (D–E, J–K) FAF reveals patchy peripheral hypoautofluorescence alternating with mottled patterns, and sharply demarcated central zone of marked hypoautofluorescence corresponding to the macular retinal pigment epithelium and choriocapillaris atrophy.

perturbation of this interface may compromise subunit interactions or alter conformational dynamics, potentially affecting enzyme function. The positional information of codon p.140Val of the IDH3A protein, cDNA: c.418–420 GTA, provides a change tolerance score of 0.46, which was classified as intolerant. This position is also found in PF00180 and no variants have been described at this position, findings that support our hypothesis about its functional importance.

Comprehensive phenotypic characterization of both affected siblings using HPO terms revealed a constellation of

clinical features consistent with *IDH3A*-related RP, manifesting from early childhood (4). Although *IDH3A* is classically associated with autosomal recessive retinal dystrophy, recent studies suggest that heterozygous carriers of severe variants in metabolic or mitochondrial genes may present with mild or tissue-specific phenotypes, especially under age-related or environmental stress.

Both affected individuals developed bilateral posterior subcapsular cataracts requiring surgery at ages 45 and 49, which is clearly early compared to population standards. Their parents, both heterozygous for a likely pathogenic *IDH3A* variant, underwent bilateral cataract surgery at ages 65 and 70, respectively. This was in the low range of the population average for age-related cataracts, and furthermore, neither of them had known risk factors such as diabetes, steroid use, or trauma that could explain this early onset.

Since *IDH3A* encodes a mitochondrial enzyme essential for the mitochondrial cycle of tricarboxylic acid and that oxidative stress plays a central role in lens aging, it is reasonable to briefly mention the hypothetical possibility of a mild, subclinical impact of heterozygosity on lens metabolism. No further details were available regarding the cataracts developed by the parents.

As has been extensively detailed in other patients carrying deleterious variants of the *IDH3A* gene, macular pseudocoloboma was observed in both the proband and her brother (11). Notably, the male patient also exhibited more advanced peripheral retinal degeneration (6). A particularly striking finding was the presence of congenital color blindness in both siblings, reported since early childhood and eventually progressing to complete functional achromatopsia. The male patient currently perceives his visual environment almost entirely in grayscale. We interpret the early onset of functional color blindness as a probable consequence of incipient macular dysfunction within the phenotypic spectrum of *IDH3A*-related retinopathy, which precedes the structural macular abnormalities observed later. We therefore consider that the gene dysfunction generates a color vision disorder of probable retinal origin, which begins very early with a subclinical impairment in macular color processing.

Currently, among the 39 phenotypic terms included among those associated with genetic alterations in the loss of function of the *IDH3A* gene, the term HP:0000551 is included; Color vision defect (last accessed on the HPO website on 5 August 2025: https://hpo.jax.org/browse/gene/NCBIGene:3419). It would be interesting to define more precisely what this is, an atypical functional color blindness acquired in early childhood.

To date, only a limited number of *IDH3A*-associated RP90 cases have been reported, and phenotypic descriptions are often incomplete, with most involving homozygous pathogenic variants (5). As the number of potentially pathogenic *IDH3A* variants identified through high-throughput sequencing continues to grow, comprehensive phenotypic documentation and precise genotype—phenotype correlation will be essential to refine clinical interpretation, enhance diagnostic yield, and support the development of personalized therapeutic interventions.

Author contributions

CRediT: **Nuria Rosell-Saiz:** Investigation, Project administration, Writing – original draft; **Antonio Sierra-Rivera:** Writing – review & editing; **Jordi Tortosa-Carreres:** Writing – review & editing; **Clara Monferrer-Adsuara:** Resources, Visualization; **Javier Montero-Hernández:** Resources, Visualization; **Carmen Espinós:** Resources, Writing – review & editing; **Raquel Rodríguez-López:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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Ethical statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and the Helsinki Declaration. Written informed consent was obtained from patients for genetic diagnosis, counseling, and anonymous data disclosure.

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