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Clinical and Genetic Characterization of *RDH12*-Retinal Dystrophy in a South American Cohort

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Purpose: To characterize the largest cohort of individuals with retinol dehydrogenase 12 (*RDH12*)-retinal dystrophy to date, and the first one from South America.

Design: Retrospective multicenter international study.

Subjects: Seventy-eight patients (66 families) with an inherited retinal dystrophy and biallelic variants in *RDH12*.

Methods: Review of clinical notes, ophthalmic images, and molecular diagnosis.

Main Outcome Measures: Visual function, retinal imaging, and characteristics were evaluated and correlated.

Results: Thirty-seven individuals self-identified as Latino (51%) and 34 as White (47%). Sixty-nine individuals (88%) had Leber congenital amaurosis (LCA)/early-onset severe retinal dystrophy. Macular and midperipheral atrophy were seen in all patients from 3 years of age. A novel retinal finding was a hyperautofluorescent ring in 2 young children with LCA. Thirty-nine patients (50%) had subsequent visits, with mean follow-up of 6.8 ± 7.3 (range, 0–29) years. Eight variants (21%) were previously unreported, and the most frequent variant was c.295C>A, p.Leu99Ile, present in 52 alleles of 32 probands. Individuals with LCA homozygous for p.Leu99Ile (31%) had a later age of onset, a slower rate of best-corrected visual acuity decrease, the largest percentage of patients with mild visual impairment, and were predicted to reach legal blindness at an older age than the rest of the cohort.

Conclusions: By describing the largest molecularly confirmed cohort to date, improved understanding of disease progression was possible. Our detailed characterization aims to support research and the development of novel therapies that may have the potential to reduce or prevent vision loss in individuals with *RDH12*-associated retinal dystrophy.

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Inherited retinal disorders (IRDs) are a varied group of conditions with a wide range of effects on the visual experience.[1] There are many ways to classify IRDs: according to their prognosis, stationary versus progressive; based on their pathophysiology, that is, primarily affecting rods or cones (e.g., rod-cone versus cone-rod dystrophy); or by their causative gene. Individuals who have an IRD can become blind before 10 years of age (or even at birth), have a constricted peripheral field but preserved central vision, have dysmorphopsia and poor color discrimination, or experience longer dark adaptation only, among many other symptoms.

It is reported that > 5 million people are affected with an IRD worldwide, or approximately 1 in every 2000 individuals.[2,3] Inherited retinal disorders are the leading cause of blindness and visual disability in the working-age population of Australia and the United Kingdom.[4,5] There is often only 1 affected person per family, with variable penetrance and expression, causing notable intra- and interfamilial variability.[6] The most common IRD phenotype is retinitis pigmentosa (RP), a rod-cone dystrophy with a prevalence of roughly 1 in 3000 individuals.[7] According to different population reports, the most frequent gene causing IRDs is *ABCA4* (associated with Stargardt disease), and the second varies by region, e.g., *USH2A* in Europe/the United States, *EYS* in Japan/Southeast Asia, and *CYP4V2* in China.[2,8–10]

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Retinol dehydrogenase 12 (*RDH12*, Mendelian Inheritance in Man [MIM] *608830) is a gene expressed in retinal photoreceptors, involved in metabolizing unstable compounds (e.g., free excessive all-trans retinal and its byproducts) that can lead to cellular toxicity and death.[11] Pathogenic variants in *RDH12* account for approximately 10% of children with Leber congenital amaurosis (LCA)/early-onset severe retinal dystrophy (EOSRD) in the Western population, and far fewer cases of RP, macular dystrophy (MD), and cone-rod dystrophy (CORD).[12–14] The classic LCA/EOSRD phenotype is characterized by a severe, widespread retinal dystrophy, with early macular atrophy and blindness before the third decade of life.[15]

Inherited retinal dystrophies is a fast-growing field, with > 300 papers published in the last 5 years (https://pubmed.ncbi.nlm.nih.gov/?term=%22inherited+retinal+disease%22&sort=date). The decreased cost of genetic testing, advances in bioinformatics, availability of multimodal ultrahigh resolution retinal imaging, and development of gene therapy have facilitated deep phenotyping studies and the delineation of genotype–phenotype correlations, increasing our understanding of these complex diseases, and ultimately contributing toward the development of the first-in-human gene therapy for an eye disease. This ever-growing knowledge represents a hopeful horizon for patients with these rare diseases.

North America and Europe are leader regions in terms of peer-reviewed research, where most of the well-characterized patients live, hence, where the majority of ongoing clinical trials and natural history studies take place. The study herein characterizes the largest cohort of individuals with *RDH12*-retinal dystrophy to date, and the first one from South America.

Methods

This project is a retrospective consecutive case series of individuals evaluated at São Paulo and Rio de Janeiro (Brazil), Santiago de Chile (Chile), various departments and cities in Colombia (Bogotá, Cundinamarca, Antioquia, Atlántico, and Norte de Santander), Trinidad (Bolivia), Caracas (Venezuela), and multiple centers and provinces throughout Argentina (Buenos Aires, Córdoba, La Pampa, Tucumán, and San Luis). Individuals that were diagnosed with a retinal dystrophy and were found to have biallelic variants in *RDH12* were included. Their medical records were reviewed at each institution and informed consent was obtained. Ethical approval was provided by the local ethics committees and the study honored the tenets of the Declaration of Helsinki.

Clinical details and relevant imaging were reviewed from each individual. Age of onset corresponds to the age individuals or their parents started noticing visual disturbances. Best-corrected visual acuity (BCVA) was converted to logarithm of the minimum angle of resolution (logMAR) for descriptive statistics. Count fingers vision was given a value of logMAR 1.98, hand motion logMAR 2.28, light perception logMAR 2.7, and no light perception logMAR 3.[16] Asymmetric BCVA was defined as a difference ≥ 0.3 logMAR (equivalent to 15 ETDRS letters) between eyes. Individuals were categorized using the World Health Organization visual impairment criteria, which define no or mild visual impairment as BCVA ≤ 0.48 (6/18, 20/60), moderate impairment as BCVA > 0.48 and ≤ 1.0 (6/60, 20/200), severe as BCVA > 1.0 and ≤ 1.3 (3/60, 20/400), and blindness as BCVA > 1.3. Records of visual field were limited within our cohort; therefore, we only took into consideration BCVA to classify patients.

Further clinical assessments consisted of dilated retinal examination, spectral domain-OCT (Heidelberg Spectralis, Heidelberg Engineering, Inc), fundus autofluorescence (Heidelberg Spectralis and Optos PLC), and color fundus photography (Topcon and Optos PLC). Normal OCT thickness in adults was extracted from Invernizzi et al[17] and in children, from Turk et al.[18] Full-field electroretinogram (ERG) testing was available for a subset of patients, performed incorporating the International Society for Clinical Electrophysiology of Vision standards.[19]

DNA was extracted from whole blood and genetic testing was performed using targeted next-generation sequencing, whole-exome sequencing, or whole-genome sequencing in each of the participant countries. When possible, blood samples were taken from parents for variant segregation analysis. Previously unreported variants were analyzed (Table S1, available at www.ophthalmologyretina.org). The pathogenicity of all variants was determined according to the guidelines of the American College of Medical Genetics and Genomics.[20]

Statistical Methods

GraphPad Prism 8.0.2 (GraphPad Software) was used for statistical analysis. The threshold of significance was set at $P < 0.05$. Linear regressions and *t* tests were used for parametric variables assessment (Figure 1A). Welch's *t* test was employed when the sample sizes were significantly different (Figure 1B). Kaplan–Meier survival curves were used to determine the age at which patients would reach legal blindness based on visual acuity (VA; > 1 logMAR with both eyes, Figure 1C).

Results

Demographics, Phenotype, and Disease Onset

Seventy-eight individuals from 66 families were included in this study and characterized (Table 2). Thirty-nine were female (50%), 37 were male (47%), and sex was not available for 2 patients. Seventy-two patients reported their ethnicity (92%): 37 self-identified as Hispanic or Latino (51%), 34 as White (47%), and 1 as Arab. Ten pedigrees had consanguinity (15%, 7 from Brazil), with parents or grandparents' first cousins. Positive family history was reported by 14 probands.

Sixty-nine individuals (88%) had LCA/EOSRD, 5 (6%) had RP, 2 (3%) had CORD, and 2 (3%) had MD. Focusing on those with EOSRD/LCA, mean (± standard deviation) age at symptoms onset was 4.3 ± 3.8 (median, 3) years. Individuals with RP had disease onset in the third decade of life (22 and 26 years old), and 1 of the individuals with MD had visual disturbances from age 30. Twenty-five individuals recalled first noticing decreased acuity (32%), 15 nyctalopia (19%), 10 concurrent nyctalopia and decreased acuity (13%), and the remaining noticed less frequent symptoms such as nystagmus, visual field loss, and strabismus.

VA

Individuals with LCA/EOSRD. Mean (± standard deviation) age at the baseline visit was 17.8 ± 11.9 years (median, 15; range, 6 months to 45). Forty-one (59%) were children (26 [38%] ≤ 10 years old), and 28 (41%) were adults (≥ 18 years old). Mean baseline BCVA was available for 63 patients (91%) and was 1.2 ±

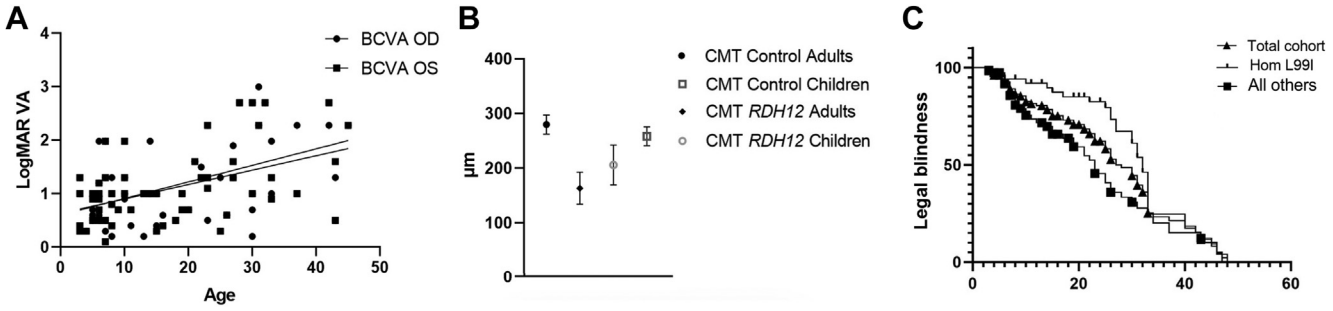

Figure 1. Statistical analysis of functional and structural parameters in patients with early-onset severe retinal dystrophy (EOSRD) from our cohort. **A,** Analyzed cross-sectionally at the initial visit, there was a significant association between age and best corrected visual acuity (BCVA) in the right eye (OD) and left eye (OS) ($P = 0.001$, $R^2 = 0.2$). **B,** Central macular thickness (CMT) in adults and children with retinol dehydrogenase 12 (*RDH12*)-EOSRD was significantly lower compared with the unaffected adults (280.1 ± 17.5 µm, $P < 0.001$) and children (258.6 ± 17.2 µm, $P < 0.001$). CMT in adults was also significantly lower than in children (OD: $P = 0.04$; OS: $P = 0.001$). **C**, Kaplan–Meier curve estimates that the percentage of patients with legal blindness (> 1 logarithm of the minimum angle of resolution [logMAR]) in the total cohort (line with triangles) will be 50% at 27 years old. In the subgroup of patients homozygous for p.Leu99Ile variants (plain line), 50% at 32 years old; and in the rest of the cohort (line with squares), 50% at 23 years old. There was a statistically significant difference between the curve for individuals with homozygous p.Leu99Ile and the one for rest of the cohort ($P = 0.005$), but not between the p.Leu99Ile group and the total cohort ($P = 0.07$), or between the one for the remaining cohort and the total group ($P = 0.15$). VA = visual acuity.

0.7 logMAR (right eye [OD] and left eye [OS]; Snellen equivalent, 20/300 ± 20/100; median, 1 [20/200]). Separating this group into individuals homozygous for p.Leu99Ile (n = 24; mean age, 21.3 ± 11.8 years) and the rest of the patients with LCA (n = 45; mean age, 15.1 ± 11.5 years), mean baseline BCVA was 1.2 ± 0.8 logMAR (OD) and 1.08 ± 0.6 logMAR (OS), whereas it was 1.1 ± 0.7 logMAR for the remaining patients. There was not a significant difference between these groups ($P = 0.3–0.64$).

Nine patients had mild visual impairment (7 pediatric), 33 had moderate (22 pediatric), 10 had severe (5 pediatric), and 12 were blind (1 pediatric). Asymmetric BCVA was seen in 19 patients (28%).

Twenty-seven individuals (39%) had mild refractive error (> −3 and < +3 diopters [D]), 8 (12%) had moderate hyperopia (≥ +3 D and < +6 D), and 3 (4%) had moderate myopia (≤ −3 D and > −6 D). Analyzed cross-sectionally at the initial visit, there was a significant association between age and BCVA OD and OS ($P = 0.001$, $R^2 = 0.2$, Fig 1A). Separating this group in individuals homozygous for p.Leu99Ile and the rest of the patients with LCA, the association remains significant in each group ($P = 0.02$ and $P = 0.003$, respectively).

Individuals with RP. Mean age (± standard deviation) at the baseline visit was 39 ± 5.2 (range, 33–46) years. Mean baseline BCVA (OD and OS) was 0.95 ± 0.5 logMAR (median, 1), 1 individual did not have visual impairment, 2 had moderate impairment, and 1 was blind. One patient had moderate myopia and 1 had mild refractive error.

Individuals with MD/CORD. Mean age at the baseline visit was 35.25 ± 10 (range, 21–46) years. Baseline BCVA (OD and OS) was 0.6 ± 0.4 logMAR (median, 0.5), 1 individual did not have visual impairment, 2 had moderate, and 1 had severe impairment. Two patients had mild refractive error.

Clinical Examination, Retinal Imaging, and Electrophysiology

Nine individuals with LCA and 2 with RP had lens opacities at baseline in ≥ 1 eye (14%), from 14 years of age.

Macular and midperipheral atrophy were seen in all individuals, from 3 years of age (Fig 2A, B), with a severe presentation of macular coloboma-like abnormality ("pseudocoloboma") in 24 individuals with LCA (35%). Bone-spicule-like pigment deposits were observed in individuals aged ≥ 5 years with RP and LCA; these deposits were denser in the midperiphery, progressing both centrifugal and centripetally (Fig 2C–E). The participants with MD (indentification [ID] 4, 57) presented with a mild, foveal-sparing maculopathy (Fig 2F), and those with CORD had a Stargardt-like phenotype. Para-arteriolar retinal pigment epithelium (RPE) preservation was seen in 1 individual with RP and 4 with LCA (ID 13, 14, 15, 20, and 21; Fig 2G).

Fundus autofluorescence imaging (available in 19 individuals with LCA, 1 with RP, and 2 with MD) was characterized by hypoautofluorescence at the posterior pole and midperiphery in all individuals with LCA and RP. A hyperautofluorescent ring was seen at the posterior pole in the 2 patients with MD and in 2 patients with LCA at ages of 3 and 6 years (Fig 2A). Peripapillary sparing was seen in patients with all phenotypes from ages 5 to 43 years.

Twenty-two individuals with LCA (32%) had electrophysiological assessments; 16 had a flat ERG, with abolished cone and rod responses (age range, 3–39 years), 5 had reduced amplitude or increased implicit time photopic waveforms and flat scotopic traces (age range, 3–19 years, 3 with homozygous p.Leu99Ile variants), and 1 individual had reduced yet present cone and rods waveforms and preserved cone flicker at age 13 (ID 34).

Macular OCT Analysis

Twenty-nine individuals (37%) had macular bilateral OCT scans at a mean age of 24.3 ± 14.5 years (Fig 3); 26 with LCA/EOSRD, 2 with RP, and 1 with MD.

Individuals with LCA/EOSRD. Nine individuals had a complete loss of structure, with RPE break and a macular "pseudocoloboma" (age range, 21–58 years). One individual had bilateral cystic macular edema at age 13, and 2 had an epiretinal membrane in ≥ 1 eye (22 and 31 years old).

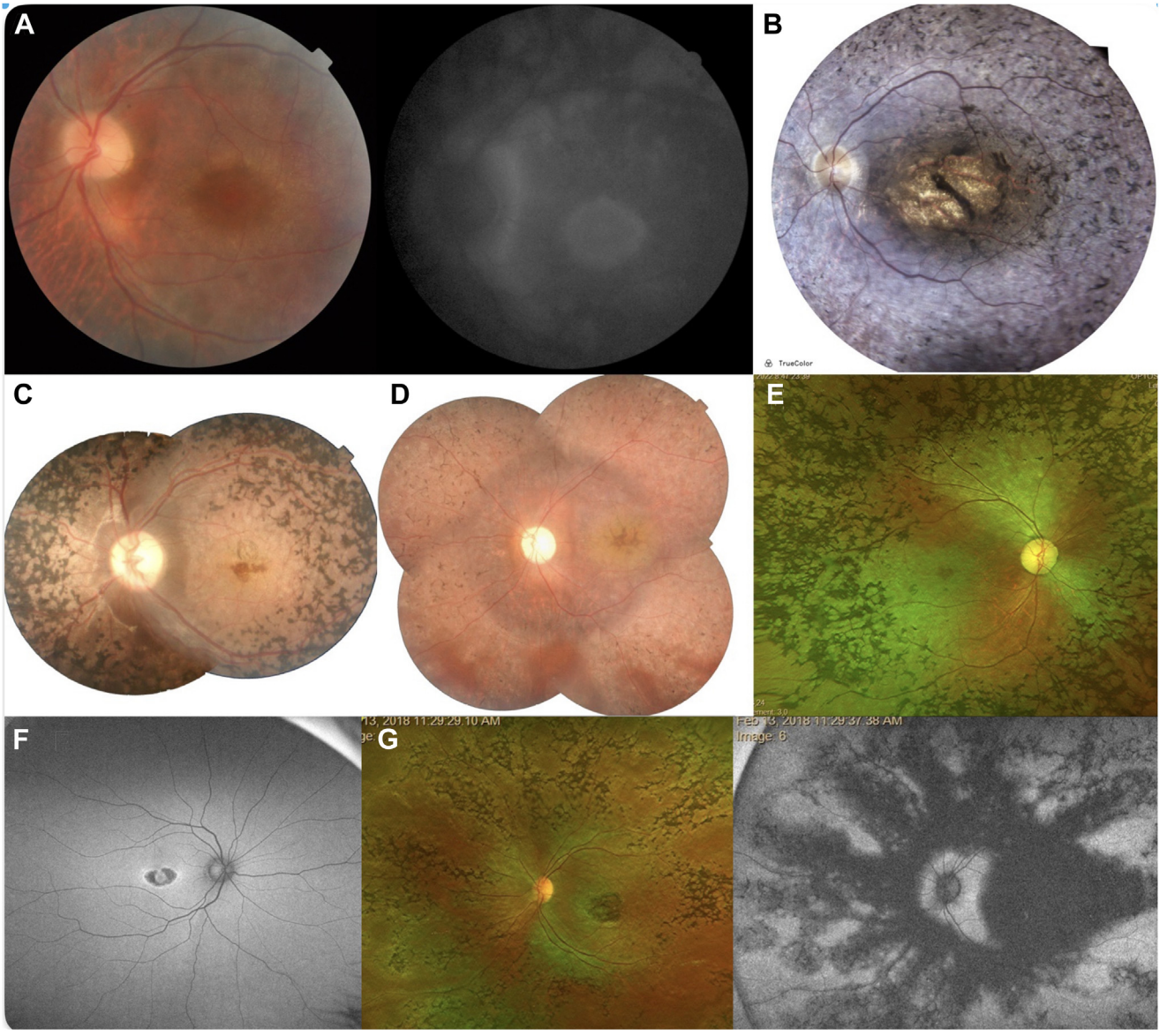

Figure 2. Retinal features of *RDH12*-retinopathy. **A,** Color and autofluorescence (AF) fundus imaging of 6-year-old patient with early-onset severe retinal dystrophy (EOSRD) (identification [ID] 47). We can see early macular dystrophy (MD) and hypoAF at the posterior pole, with a hyperAF ring demarcating the outer limit of the MD and peripapillary sparing. **B,** Twenty-two-year-old patient (ID 9) with EOSRD and severe, petaloid macular atrophy and bone-spicule-like (BSL) pigment in the midperiphery. **C,** Dense BSL pigment and relatively mild MD in a 7-year-old patient with EOSRD (ID 3). **D,** Eight-year-old patient (ID 5) with EOSRD, with minimal BSL pigment, early MD, and vessel attenuation. **E,** Twenty-five-year-old patient with EOSRD, homozygous for p.Leu99Ile (ID 33), with a milder presentation, BSL pigment, and early macular dystrophy. **F,** Thirty-year-old participant with MD (ID 4), with a foveal-sparing maculopathy and preserved retinal periphery. **G,** Seventeen-year-old participant with EOSRD (ID 15), with para-arteriolar retinal pigment epithelium preservation, possibly representing an early watercolor-like variegated pattern.

Quantitative measurements were available in 32 eyes (16 from children). Mean central macular thickness (CMT) of the adults was 163.5 ± 29.3 μm (OD) and 151 ± 38 μm (OS), and 206 ± 36.6 μm (OD) and 211.9 ± 23.3 μm (OS) for children. A continuous subfoveal ellipsoid zone was present bilaterally in 9 patients (age range, 3−17 years; 4 homozygous for p.Leu99Ile), and measured 208 ± 30 μm.

Central macular thickness was significantly lower compared with the unaffected adults (280.1 ± 17.5 μm, $P < 0.001$) and children (258.6 ± 17.2 μm, $P < 0.001$, Fig 1B).[17,18] Central macular thickness in adults was also significantly lower than in children ($P = 0.04$ [OD] and $P = 0.001$ [OS]). There was not a significant association between age and CMT in adults ($P = 0.3$) or in children ($P = 0.2$). Best-corrected visual acuity was not significantly associated with CMT ($P = 0.8$).

Individuals with RP and MD/CORD. Macular OCT scans from the 2 individuals with RP were acquired at 31 and 32 years of age; they did not have a measurable subfoveal ellipsoid zone line and had decreased mean CMT when compared with the general population (203 ± 6 μm).

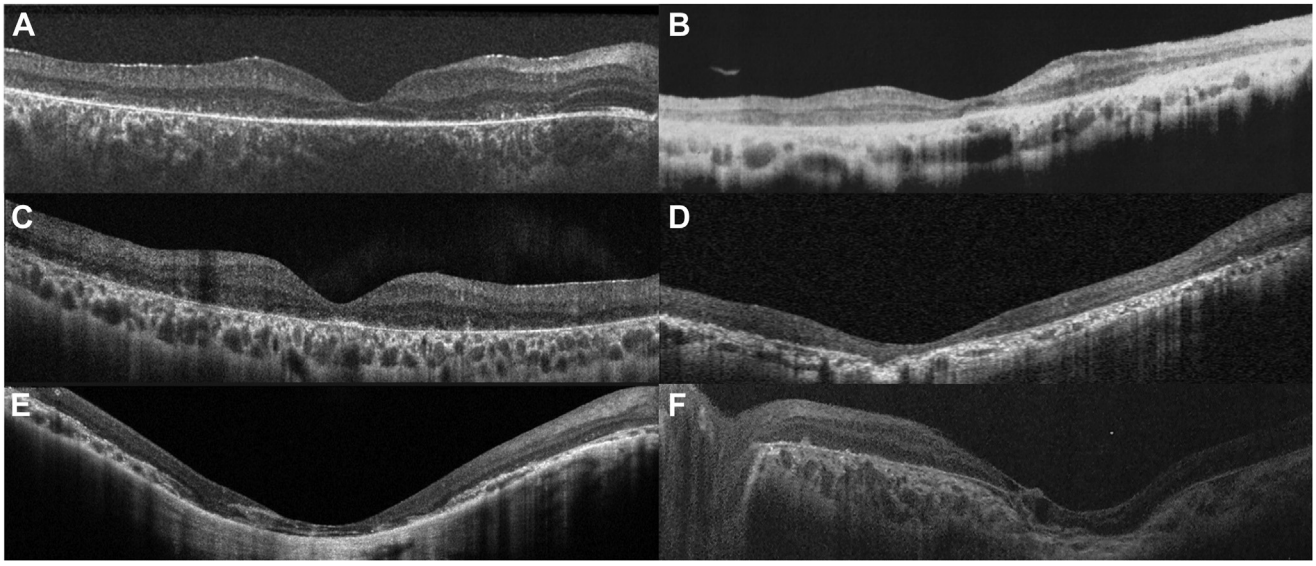

Figure 3. Macular OCT in *RDH12*-early-onset severe retinal dystrophy (EOSRD). Patients **A**–**D** are homozygous for the p.Leu99Ile variant. **A,** Foveal scan of right eye (OD) of a 5-year-old patient (identification [ID] 21), with preserved overall architecture, yet only a nasal remanent of ellipsoid zone (EZ). **B,** Right eye from a 19-year-old patient (ID 32) with parafoveal atrophy and a subfoveal island of EZ line. **C,** Left eye (OS) from a 25-year-old patient (ID 33) with maintained macular architecture and no visible EZ line. **D,** OD from a 35-year-old patient (ID 2) with thinned macula and a discontinuous retinal pigment epithelium (RPE) temporal to the fovea. **E,** OD of a 22-year-old patient (ID 9) with macular peudocoloboma, temporal discontinuous RPE, and nasal subretinal fibrosis. **F,** OS of a 29-year-old male (ID 8) with macular pseudocoloboma, loss of retinal architecture, and thinned RPE.

The individual with MD (ID 4) had a fovea-sparing maculopathy with preserved subfoveal ellipsoid zone at 33 years old and decreased CMT (128 μm [OD] and 133 μm [OS]).

Longitudinal Analysis

Thirty-nine individuals (50%) had follow-up visits, with a mean follow-up time of 6.8 ± 7.3 (range, 0–29, median, 4) years, and mean age at final visit of 23.8 ± 13.7 years (age range, 4–52; median, 24; 14 still in pediatric age). Twenty-five individuals had LCA, 2 RP, 1 MD, and 1 CORD.

Individuals with LCA/EOSRD. Final BCVA (OD and OS) was 1.24 ± 0.7 logMAR (20/348 ± 20/100) (median, 1 [20/200]). The rate of BCVA decline was 0.02 logMAR (1 letter)/year and there was not a significant difference between baseline and follow-up BCVA (P = 0.4). Twelve individuals (48%) lost ≥ 15 ETDRS letters over follow-up in 1 or both eyes (after 2–29 years). Eleven individuals (44%) progressed to more advanced World Health Organization categories of visual impairment over follow-up, 5 of whom became blind (age range, 21–48). Kaplan–Meier analysis of individuals with LCA predicted that at 27 years of age, 50% of the patients will reach legal blindness based on VA (> 1 logMAR, Fig 1C).

Individuals with RP and MD/CORD. The 2 patients with CORD and MD were followed for 6 years and 1 year, respectively, and they both remained in the same category of visual impairment. The 2 patients with RP were assessed over 6 and 7 years and progressed to severe impairment and blindness at a latest age of 52 and 40 years old.

Molecular Diagnosis

All individuals had biallelic variants in *RDH12*; affected individuals from 31 families had homozygous variants, and 35 were compound heterozygous. Thirty-eight different variants were present in our cohort: 29 missense, 4 small frameshift deletions and duplications, 1 in-frame indel, 3 splice-site alteration, and 1 nonsense (Table 2).

Thirty variants (79%) were present in the literature,[21–31] and 8 (21%) were previously unreported (Fig 4, Table S1). Among the latter, 1 was classified as pathogenic, 5 as likely pathogenic, and 2 as variants of uncertain significance. The most frequent variant was c.295C>A, p.Leu99Ile, present in 52 alleles of 32 probands (allele frequency of 39%); followed by c.806_810del, p.Ala269Glyfs*2, present in 15 alleles of 11 probands (allele frequency of 11%); and c.278T>C, p.Leu93Pro, present in 13 alleles of 10 probands (allele frequency of 10%).

Seven families (11%) had double-null (DN) genotypes (nonsense, frameshift, or splice-site), and 59 (89%) were not double-null (NDN). Two individuals (ID 34 and 35) had a pathogenic variant in trans with a variant of uncertain significance; they were included in the cohort and considered as likely *RDH12*-related cases. The patient with the homozygous variant p.Arg234His (ID 4) was also homozygous for c.-123C>T.

Genotype–Phenotype Correlation

Twenty-five individuals (32%) were homozygous for the presumed milder variant p.Leu99Ile,[32] 24 with LCA/EOSRD and 1 with RP. Forty-four were the remaining NDN, and 9 were DN (8 with LCA/EOSRD and 1 with RP). Only individuals with LCA/EOSRD were considered for the following analysis, given that the remaining subgroups were too small to perform relevant comparisons. Mean age of onset was 3.7 ± 3.8 years for the NDN, 3.5 ± 2.8 years for the DN, and 5.6 ± 4.7 years for the p.Leu99Ile homozygous (no significant differences, P = 0.07–0.7). Best-corrected visual acuity at a mean age of 20 years old was 1.1 ±

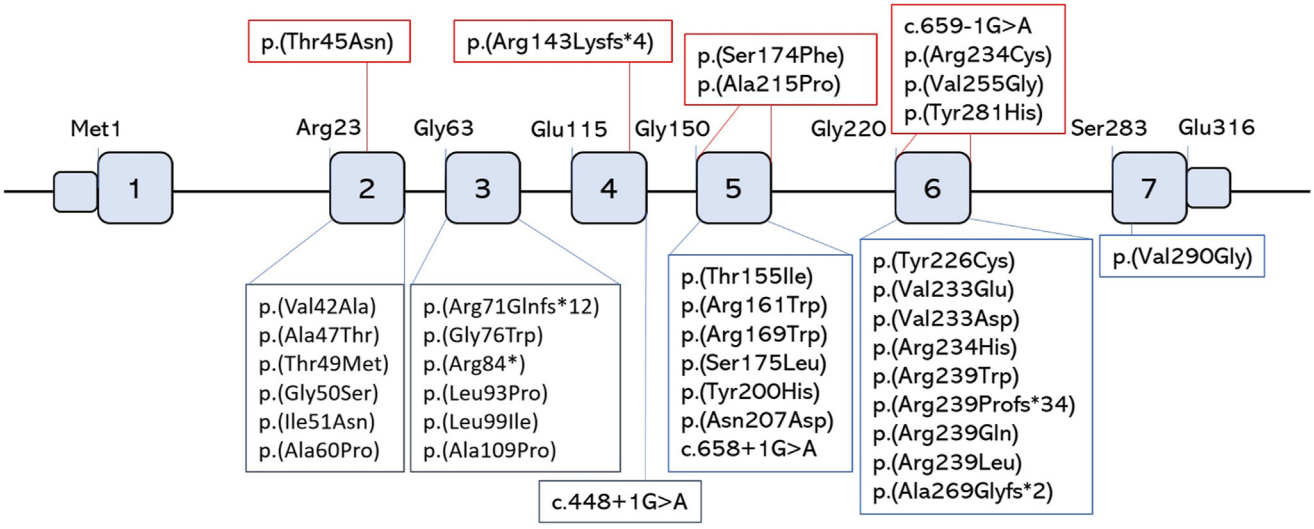

Figure 4. Graphic representation of the *RDH12* gene and the variants in this cohort. The 7 exons and their boundaries are detailed. Variants displayed below the gene are already reported in the literature, and those above are the previously unreported ("novel") variants described in this study.

0.6 logMAR for NDN and individuals with homozygous p.Leu99Ile, and 1.6 ± 0.9 logMAR for DN ($P = 0.09$). Five patients from the homozygous p.Leu99Ile subgroup had none or mild impairment, compared with 1 from NDN, and none from DN.

The rate of VA decline was 0.02 logMAR (1 letter)/year for the p.Leu99Ile group, and 0.03 logMAR (1.5 letters)/year in the remaining NDN participants (the DN had only 2 patients with follow-up BCVA). Kaplan–Meier analysis of individuals with LCA predicted that 50% of the patients with homozygous p.Leu99Ile will reach VA-based legal blindness at 32 years of age, whereas the rest of the cohort will do so at 23 years old (Fig 1C). There was a statistically significant difference between the curve for individuals with homozygous p.Leu99Ile and the curve for rest of the cohort ($P = 0.005$), but not between the p.Leu99Ile group and the total cohort ($P = 0.07$), or between the curve for the remaining cohort and the total group ($P = 0.15$). The 5 individuals with LCA who progressed to the World Health Organization blindness category were all nonhomozygous for p.Leu99Ile.

No significant differences were found regarding fundus features. Nine of the 15 individuals with flat ERG were homozygous for p.Leu99Ile (age range, 6–39 years), 6 were NDN, and 1 was DN. Two of the 5 with present photopic waveforms belonged to the p.Leu99Ile subgroup, the remaining 3 were NDN, and the individual with both scotopic and photopic traces present was NDN.

Three young patients were homozygous for p.Leu93Pro, all with none or mild visual impairment in their first and second decade of life.

Discussion

The South American population with IRD is largely understudied and poorly represented in peer-reviewed research. Single-country reports characterizing specific conditions exist;[21,33,34] however, comprehensive regional data are scarce. In this study, some of the most populated countries of the continent collaborated to describe the phenotypic and genotypic landscape of *RDH12*-retinal dystrophy in South America, report "novel" variants, and explore genotype–phenotype correlations.

The phenotype was consistent with previous reports, with a wide spectrum of severity and phenotypes ranging from MD to LCA.[35] Early maculopathy was the most common feature in all individuals, as described in smaller cohorts.[12,29] Peripapillary sparing (clearly distinguishable in color and fundus autofluorescence images, Fig 2A–D) was also a prevalent feature, as well as midperipheral RPE atrophy with bone-spicule-like pigmentation, consistent with former descriptions.[36,37] A macular hyperautofluorescent ring was detected for the first time in *RDH12*-LCA/EOSRD (Fig 2A), in 2 young individuals. By analysis of accompanying OCT, this ring appeared to be demarcating the outer limit of an area of affected retina, unlike the one seen in *CEP20*- or *RPE65*-LCA, which demarcates the area of preserved outer layers.[38] The para-arteriolar RPE preservation, as seen in *CRB1*-retinopathy, was previously reported by Mackay et al.[29,39] This pattern is also seen in some cases of *RDH12*-retinopathy with a watercolor-like, variegated pattern.[32]

RDH12 p.Leu99Ile is presumed to be a founder mutation and it has been associated with LCA and RP phenotypes.[22,25,40] It is enriched in the Latino population, with a frequency of 0.0003 (https://gnomad.broadinstitute.org), and was seen as a recurrent variant among Mexican individuals with IRDs.[41] In our cohort, it was present in patients from Argentina, Colombia, Chile, Venezuela, and Brazil, in both the homozygous and heterozygous state. It has previously been associated with a possibly milder phenotype with early onset (1.5–3 years old) and preserved BCVA into adulthood; however, this was based on only 3 Spanish individuals.[32] Functional testing indicated a residual 10% enzymatic activity in an in vitro

Table 2. Clinical, Genetic, and Imaging Characteristics of Patients with *RDH12*-Retinal Dystrophy

ID	Country	Phenotype	Consanguinity	Gender	Population	Age at First Symptoms	Age at First Visit	Presenting VA (OD, OS)		ERG Result (Age)	Fundus Characteristics	Genotype			
1	Argentina	LCA	Y	M	White	1	8	1.3	1		MA at 8 yo, BSL 360°	c.716G>T	p.Arg239Leu	c.716G>T	p.Arg239Leu
2*	Argentina	EOSRD	N	F	White	10	37	2.28	1.0		Dense BSL and MA	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
3	Argentina	LCA	N	F	White	4	7	1.98	1.98		Dense BSL 360°, blunted macula	c.295C>A	p.Leu99Ile	c.464C>T	p.Thr155Ile
4	Argentina	MD	N	M	Latino	30	31	0.1	0.1		Foveal-sparing maculopathy	c.701G>A, c.-123C>T	p.Arg234His, p.?	c.701G>A, c.-123C>T	p.Arg234His, p.?
5	Argentina	LCA	N	m	White	0.5	9	0.7	0.7		MA with few BSL	c.464C>T	p.Thr155Ile	c.716G>T	p.Arg239Leu #
6	Argentina	EOSRD	N	M	Latino	11	7	0.30	0.10	Flat (13)	MA and BSL 360°	c.278T>C	p.Leu93Pro	c.278T>C	p.Leu93Pro
7A	Argentina	LCA	N	M	White	3	18	0.50	0.50		MA with few BSL	c.278T>C	p.Leu93Pro	c.148G>A	p.Ile51Asn #
7B	Argentina	EOSRD	N	F	White	11	15	1	1		Bilat MA, pigmented BSL	c.278T>C	p.Leu93Pro	c.148G>A	p.Ile51Asn #
8	Bolivia	LCA	N	M	Latino	3	29	0.70	1		Macular pseudocoloboma	c.278T>C	p.Leu93Pro	c.716G>A	p.Arg239Gln
9	Argentina	LCA	N	F	White	0.1	10	1	1		Macular pseudocoloboma	c.524C>T	p.Ser175Leu	c.806_810del	p.Ala269Glyfs*2
10	Argentina	LCA	N	M	Latino	3	42	2.28	2.7	Flat (4)	MA OS	c.278T>C	p.Leu93Pro	c.464C>T	p.Thr155Ile
11	Argentina	LCA	N	F	White	3	19	1	1	Flat (4)	Severe BSL and macular scar	c.806_810del	p.Ala269Glyfs*2	c.152T>A	p.Ile51Asn #
12A*	Chile	LCA	N	M	Latino	5	30	1	1	Flat (28)	Macular pseudocoloboma, BSL in midperiphery	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
12B*	Chile	LCA	N	M	Latino	4	30	1	1	R flat C reduced (19)	Macular pseudocoloboma, BSL in midperiphery	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
13*	Chile	RP	N	M	Latino	26	46	0.8	1.3		Macular pseudocoloboma, BSL and PPRPE	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
14*	Chile	LCA	N	F	Latino	0.1	8	0.8	0.8		Macular pseudocoloboma, BSL and PPRPE	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
15*	Chile	LCA	N	F	Latino	0.1	20	0.7	0.7	Flat (20)	Macular pseudocoloboma, BSL and PPRPE	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
16A*	Chile	LCA	N	F	Latino	0.1	32	2.7	2.7			c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
17*	Chile	EOSRD	N	M	Latino	10	27	1.3	1.3		Macular pseudocoloboma, BSL in midperiphery	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
16B*	Chile	EOSRD	N	M	Latino	10	25	1.3	0.3		Macular pseudocoloboma, BSL in midperiphery	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
18*	Chile	EOSRD	N	F	Latino	11	31	3	2.28		Macular pseudocoloboma, BSL in midperiphery	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
19	Chile	LCA	Y	F	Arabic	0.1	23	2.28	1.1		Macular pseudocoloboma, BSL in midperiphery	c.715dupC	p.Arg239Profs*3	c.715dupC	p.Arg239Profs*34
20	Chile	LCA	N	F	Latino	0.1	8	0.2	0.4	R flat C reduced (5)	Macular pseudocoloboma, BSL and PPRPE	c.295C>A	p.Leu99Ile	c.716G>T	p.Arg239Leu #
21*	Chile	LCA	N	M	Latino	3	3	0.3	0.3	R flat C reduced (3)	Macular pseudocoloboma, BSL and PPRPE	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
22*	Chile	LCA	N	F	Latino	0.1	3	1	1		Macular pseudocoloboma	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
23A*	Colombia	EOSRD	N	F	Latino	13	33	1.98	1.3	Flat (39)	Macular pseudocoloboma and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
23B*	Colombia	LCA	N	M	Latino	NA	14	1.98	1		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
24A	Colombia	LCA	N	F	Latino	3	NA					c.295C>A	p.Leu99Ile	c.481C>T	p.Arg161Trp #
24B	Colombia	EOSRD	N	M	Latino	8	23	2.28	2.28	R flat C reduced (11	MA and BSL 360°	c.295C>A	p.Leu99Ile	c.481C>T	p.Arg161Trp #
25A*	Colombia	EOSRD	N	M	Latino	7	14	1	1	Flat (16)	MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
25B*	Colombia	LCA	N	M	Latino	4	13	0.2	1	Flat (14)	Macular pseudocoloboma and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
26A	Colombia	EOSRD	Y	M	Latino	6	11	0.4	0.7		Macular pseudocoloboma, BSL in midperiphery	c.250C>T	p.Arg84*	c.250C>T	p.Arg84*
26B	Colombia	EOSRD	Y	M	Latino	9	30	2.7	2.7		MA and BSL 360°	c.250C>T	p.Arg84*	c.250C>T	p.Arg84*
27	Colombia	LCA	N	M	Latino	3	31	2.28	2.28	Flat (6)	MA and BSL 360°	c.139G>A	p.Ala47Thr	c.643G>C	p.Ala215Pro #
28*	Colombia	EOSRD	N	F	Latino	15	6	0.5	0.5		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
29A	Colombia	LCA	N	F	Latino	2	33	1	0.9	Flat (25)	MA and BSL 360°	c.806_810del	p.Ala269Glyfs*2	c.146C>T	Thr49Met #
29B	Colombia	EOSRD	N	F	Latino	7	19	1	0.7		Macular pseudocoloboma, BSL in midperiphery	c.806_810del	p.Ala269Glyfs*2	c.146C>T	Thr49Met #
30A*	Colombia	LCA	N	F	Latino	2	10	1.3	1.3	Flat (9)	MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
30B*	Colombia	LCA	N	M	Latino	2	22	1.5	1.3	R flat C reduced (18	MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
31*	Colombia	EOSRD	N	M	Latino	7	NA					c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
32*	Colombia	LCA	N	M	Latino	4	4	0.3	0.3	Flat (9)	MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
33*	Colombia	LCA	N	F	Latino	3	15	0.3	0.3		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
34	Colombia	EOSRD	N	F	Latino	11	15	0.4	0.3	R&C reduced (14)	MA and BSL 360°	c.295C>A	p.Leu99Ile	c.764T>G	p.Val255Gly #

(*Continued*)

Table 2. (Continued.)

ID	Country	Phenotype	Consanguinity	Gender	Population	Age at First Symptoms	Age at First Visit	Presenting VA (OD, OS)		ERG Result (Age)	Fundus Characteristics	Genotype			
35	Brazil	LCA	N	F	White	NA	43	0.5	0.5		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.841T>C	p.Tyr281His
36	Brazil	LCA	Y	F	White	3	5	0.5	0.5		MA and BSL 360°	c.806_810del	p.Ala269Glyfs*2	c.806_810del	p.Ala269Glyfs*2
37	Brazil	RP	Y	F	White	22	42	1.6	1.6		Macular pseudocoloboma, BSL in midperiphery	c.805_809del	p.Ala269Glyfs*2	c.805_809del	p.Ala269Glyfs*2
38	Brazil	LCA	N	M	White	3	45	2.28	2.28		Macular pseudocoloboma and BSL 360°	c.658+1G>A	NA	c.521C>T	p.Ser174Phe
39	Brazil	LCA	N	F		0.1	10	0.9	1.98			c.698T>A	p.Val233Asp	c.806_810del	p.Ala269Glyfs*2
40A	Brazil	RP	N	M		NA	35	0.3	0.1			c.278T>C	p.Leu93Pro	c.295C>A	p.Leu99Ile #
40B	Brazil	RP	N	F		NA	NA				MA and BSL with watercolor-like pattern	c.278T>C	p.Leu93Pro	c.295C>A	p.Leu99Ile #
41	Brazil	LCA	N	M	White	0.1	23	0.5	1.3		Macular pseudocoloboma and BSL 360°	c.146C>T	p.Thr49Met	c.659-1G>A	NA
42	Brazil	EOSRD	N	F	White	11	6	0.6	0.9	Flat (9)	Macular pseudocoloboma, BSL in midperiphery	c.598T>C	p.Tyr200His	c.146C>T	p.Thr49Met
43	Brazil	LCA	Y	M	White	0.1	NA				Macular pseudocoloboma, BSL in midperiphery	c.226G>T	p.Gly76Trp	c.226G>T	p.Gly76Trp
44*	Brazil	LCA	Y	F	White	2	43	1.3	1.6		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
45	Brazil	LCA	N	NA		NA	NA					c.806_810del	p.Ala269Glyfs*2	c.698_699delinsAA	p.Val233Glu #
46	Brazil	LCA	Y	M	White	2	7	1.3	1.3		MA and BSL 360°	c.698_699delinsAA	p.Val233Glu	c.698_699delinsAA	p.Val233Glu
47	Brazil	LCA	N	M	White	5	5	0.7	0.9		MA	c.278T>C	p.Leu93Pro	c.278T>C	p.Leu93Pro
48	Brazil	LCA	N	F	Latino	3	6	1.98	1		MA	c.698T>A	p.Val233Asp	c.806_810del	p.Ala269Glyfs*2
49A	Brazil	LCA	N	F	White	2	6	0.6	0.7		MA and BSL 360°	c.125T>C	p.Val42Ala	c.325G>C	p.Ala109Pro #
50*	Brazil	EOSRD	Y	M	White	NA	27	1.9	1.6		Macular pseudocoloboma, BSL in midperiphery	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
51	Brazil	EOSRD	N	F	White	10	26	0.6	0.6		MA and BSL 360°	c.505C>T	p.Arg169Trp	c.278T>C	p.Leu93Pro
52	Brazil	LCA	Y	M		3	16	0.6	0.4			c.278T>C	p.Leu93Pro	c.278T>C	p.Leu93Pro
53	Brazil	LCA	N	F	White	2	3	1.3	1.3		MA and BSL 360°	c.178G>C	p.Ala60Pro	c.677A>G	p.Tyr226Cys
54A	Brazil	LCA	N	M	White	1	21	1.6	1.6		MA and BSL with watercolor-like pattern	c.806_810del	p.Ala269Glyfs*2	c.806_810del	p.Ala269Glyfs*2
54B	Brazil	LCA	N	F	White	2	7	0.5	0.5		MA and BSL 360°	c.806_810del	p.Ala269Glyfs*2	c.806_810del	p.Ala269Glyfs*2
49B	Brazil	LCA	N	F	White	2	6	1.2	1.2		MA and BSL 360°	c.125T>C	p.Val42Ala	c.325G>C	p.Ala109Pro #
55	Brazil	LCA	NA	F	White	2	28	2.7	2.7	Flat (25)	MA and BSL 360°	c.806_810del	p.Ala269Glyfs*2	c.806_810del	p.Ala269Glyfs*2
56*	Brazil	EOSRD	N	F	White	7	30	0.2	1	Flat (31)	MA and nummular pigmentation	c.295C>A	p.Leu99Ile	c.295C>A	p.Leu99Ile
57	Brazil	MD	N	F	White	NA	43	0.5	0.5		MA	c.295C>A	p.Leu99Ile	c.700C>T	p.Arg234Cys
58	Brazil	CORD	N	M	White	NA	46	1.3	1.3		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.715C>T	p.Arg239Trp
59	Brazil	RP	N	M	Latino	NA	33	1	1		MA and nummular pigmentation	c.869T>G	p.Val290Gly	c.521C>T	p.Ser174Phe
60	Brazil	LCA	N	F	White	1.9	10	1.3	1.3		MA and BSL 360°	c.210dup	p.Arg71Glnfs*12	c.698_699delinsAA	p.Val233Glu
61	Brazil	NA	N	NA		NA	NA					c.295C>A	p.Leu99Ile	c.619A>G	p.Asn207Asp
62	Brazil	CORD	N	M	White	9	21	0.6	0.5		MA and BSL 360°	c.295C>A	p.Leu99Ile	c.701G>A	p.Arg234His
63	Brazil	LCA	N	M	White	5	NA				MA and BSL 360°	c.428del	p.Arg143Lysfs*4	c.448+1G>A	NA
64	Brazil	LCA	N	M	White	0.8	5	0.6	1		MA and BSL 360°	c.806_810del	p.Ala269Glyfs*2	c.464C>T	p.Thr155Ile
65	Brazil	LCA	N	F	White	1	3	0.4	0.4		MA and BSL 360°	c.505C>T	p.Arg169Trp	c.278T>C	p.Leu93Pro
66	Venezuela	LCA	N	F	Latino	0.5	4	1.3	0.9	Flat (5)	MA and BSL	c.295C>A	p.Leu99Ile	c.134C>A	p.Thr45Asn

BSL = bone-spicule-like; C = cones; CORD = cone-rod dystophy; EOSRD = early-onset severe retinal dystrophy; ERG = electroretinogram; F = female; ID = identification; LCA = Leber congenital amaurosis; M = male; MA = macular atrophy; MD = macular dystrophy; N = no; NA = not available; OD = right eye; OS = left eye; PPRPE = preserved para-arteriole retinal pigment epithelium; R = rods; *RDH12* = retinol dehydrogenase 12; RP = retinitis pigmentosa; VA = visual acuity; Y = yes.
*Patients are homozygous for p.Leu99Ile.
#Patients had segregation analysis that confirmed that the variants are in trans.

assay (i.e., a similar reduction to most other variants), hence the reason for the less-severe phenotype remains unclear.[22] In our larger cohort of patients with p.Leu99Ile, we see that they had a later age of onset, slower rate of BCVA decrease, estimated preserved vision until older age, and were the largest percentage of patients with mild visual impairment. An ongoing parallel study is examining detailed genetic and genealogical data to uncover the origin and age of *RDH12* p.Leu99Ile.

Regarding visual function, *RDH12*-LCA/EOSRD is typically a severe retinal dystrophy with profoundly diminished ERG responses from birth/early childhood, visual impairment in infancy, and legal blindness before the third decade of life.[15] This was the case for our overall cohort; however, the subset of individuals homozygous for p.Leu99Ile were found to have relative functional foveal sparing and subsequently better maintained BCVA until the fifth/sixth decade (ID 2, 12A, 12B, 33, 56; Fig 2E). These patients are at the mildest end of the EOSRD spectrum. They may represent good candidates for future treatment trials (with a larger window of opportunity for intervention); however, they may be possibly suboptimal due to the milder presentation and relatively good functional vision until middle/later adulthood.

It is of interest that in our cohort age was significantly associated with BCVA, indicating progressively decreased vision. In *CEP290*-LCA/EOSRD, vision loss is often severe from the first decade of life, without an association with age.[42] Central macular thickness in the adults of our cohort was similar to that seen in adults with *RPE65*-EOSRD.[43,44] These findings may point at a gene supplementation strategy potentially being plausible for *RDH12*-EOSRD.

One hundred seventy-four variants are reported in *RDH12* to date (https://my.qiagendigitalinsights.com/bbp/view/hgmd, April 2023). Seventy-nine percent of the variants seen in South America were reported in the literature in other regions of the world, probably related to the diverse ethnic blend of the Latino population.[45,46] Eight previously unreported variants were identified, increasing by 4% the number of *RDH12* variants described to date, adding to the understanding of this still not fully elucidated gene.

Our study limitations include its retrospective nature, not all data being available for every individual, and data being acquired with various methods and protocols. Segregation data and detailed clinical information, including visual fields, were also limited. These are largely offset by the large number of genetically confirmed individuals, the wide geographic patient inclusion from an understudied region and ethnic background, and their wide age and phenotypic range.

We present the largest cohort of patients with *RDH12*-retinal dystrophy to date, and the first one from South America. One-third of the individuals presented with an unusual, milder phenotype associated with homozygous p.Leu99Ile, and one-third were children. The rise in gene-specific clinical trials for IRD prompts us to characterize and report the individuals with IRD-related vision impairment and blindness in our communities (*Invest Ophthalmol Vis Sci.* 63:4512−F0299, 2022). By providing this detailed information, we aim to collaborate with and extend research, and the development of novel therapies that may have the potential to reduce or prevent vision loss in individuals with *RDH12*-dystrophy.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The medical records of the individuals included were reviewed at each institution and informed consent was obtained from all participants. Ethical approval was provided by the local ethics committees and the study adhered to the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CMT** = central macular thickness; **CORD** = cone-rod dystrophy; **D** = diopters; **DN** = double-null; **EOSRD** = early-onset severe retinal dystrophy; **ERG** = electroretinogram; **ID** = identification; **IRD** = inherited retinal disorder; **LCA** = Leber congenital amaurosis; **logMAR** = logarithm of the minimum angle of resolution; **MD** = macular dystrophy; **NDN** = not double-null; **OD** = right eye; **OS** = left eye; ***RDH12*** = retinol dehydrogenase 12; **RP** = retinitis pigmentosa; **RPE** = retinal pigment epithelium; **VA** = visual acuity.

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