Characteristics and Predictors of Pediatric and Adult Patients with Inherited Retinal Degenerations: Tertiary Care Ophthalmology Clinic Data

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ABSTRACT

Introduction: Inherited retinal degenerations (IRDs) are genetically driven disorders affecting retinal photoreceptors, the retinal pigment epithelium, bipolar cells, and other retinal structures. This study aimed to compare characteristics of pediatric versus adult patients at the time of initial presentation to a tertiary care IRD clinic.

Methods: A retrospective chart review of 527 patients diagnosed with IRDs was conducted. Data collected included age at presentation, diagnosis, ocular and systemic characteristics, demographics, distance from home to the clinic, and type of referring provider.

Results: High hyperopia, high myopia, high astigmatism, congenital syndactyly, and developmental delay were more common among pediatric patients. Adult patients more frequently presented with reduced central vision, peripheral vision loss, color vision deficits, nyctalopia, flashes/floaters, cataracts, and family history of cataracts. Compared to a control population, adult IRD patients had higher rates of cardiac conditions, lower prevalence of obesity, and similar rates of diabetes. No significant differences were found in type of referring provider or proximity to the clinic.

Discussion: Distinct clinical and familial characteristics were associated with age at presentation. Pediatric patients often exhibited refractive and developmental features, while adults presented with progressive vision symptoms. Despite assumptions, geographic proximity did not significantly influence age at presentation, suggesting other barriers to care.

Conclusions: This study identifies characteristics associated with pediatric and adult presentation in patients with IRDs. Better understanding of these patterns may improve early recognition, clinician education, and timely treatment.

INTRODUCTION

Inherited retinal diseases (IRDs) represent a diverse group of genetically heterogeneous disorders characterized by dysfunction of multiple retinal structures, including photoreceptors, the retinal pigment epithelium, and associated neural layers. These disorders present with a spectrum of clinical symptoms ranging from early-onset visual impairment to progressive vision loss in adulthood. While refractive errors such as myopia and hyperopia are commonly associated, other symptoms including nyctalopia, photophobia, and developmental delays—are equally critical in pediatric presentations. To date, more than 280 genes have been implicated in IRD pathogenesis, each associated with distinct clinical phenotypes.[1] Given the diversity of IRD presentations, early identification and diagnosis are challenging.

IRDs present with a wide range of symptoms and are frequently associated with refractive errors, particularly myopia.[2] Early-onset high myopia has been linked consistently with IRDs, including retinitis pigmentosa (RP) caused by mutations in *RPGR* and *RP1*,[3-6] congenital stationary night blindness,[7] and cone dystrophy and cone-rod dystrophy.[8] High hyperopia also has been associated with IRDs, including RP[4,9] and other dystrophies.[2]

Gene-based therapies represent a promising area of research for treatment of IRDs with known monogenic variants. In 2017, voretigene neparvovec-rzyl became the first gene therapy approved by the US Food and Drug Administration for the treatment of *RPE65*-mediated IRD.[10] This landmark achieve-

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ment spurred significant international investment in research for other IRD gene therapeutics. Despite these advancements, a recent analysis of IRD knowledge identified the natural history and environmental factors as areas requiring continued research.[11] Significant knowledge gaps remain in understanding patient factors that contribute to early or delayed presentation at tertiary care centers. Further exploration of these factors is essential to ensure timely access to gene therapy and other treatments or resources.

The primary objective of this study was to compare the characteristics of patients who present for the first time to the IRD clinic in adulthood versus childhood. We hypothesized that poor visual acuity and family history would be the most predictive factors for early recognition of IRDs and that proximity to a tertiary care center would be associated with a younger age at referral compared to patients living farther away.

METHODS

Patient Inclusion

After Institutional Review Board approval (protocol number 2020-1207), we conducted a retrospective cohort study of patients of all ages diagnosed with an IRD at a single tertiary ophthalmology referral center—the Inherited Retinal Degeneration Clinic at the University of Wisconsin Department of Ophthalmology and Visual Sciences—from January 1, 1990, to January 1, 2020. All patients who presented to the clinic with IRDs who consented to participate were included in an IRB-approved REDCap database hosted at the University of Wisconsin-Madison. Inclusion criteria were a confirmed clinical or molecular diagnosis of IRD following referral. Final diagnoses were determined based on clinical examination, imaging, functional testing, and genetic testing when available. Diagnoses were cross-validated through referral notes and follow-up assessments. Exclusion criteria included patients whose initial clinic visit was not with one of the study's IRD ophthalmologists, those who did not consent to database inclusion, and those not diagnosed with IRDs.

Data Collection

A manual chart review was conducted to collect demographic information, relevant personal and family medical history, IRD diagnosis, disease characteristics, and treatment data from a single patient encounter using a standardized interview template. Demographic variables included age, sex, race (White, Black, Asian, Hispanic, Native American, other), education (high school or less, bachelor's degree, graduate degree, not applicable [N/A]), driving status, employment status, and home address. Each patient's home address and the clinic address were used to estimate commute distance (<20, 20-80, >80 miles) using Google Maps (Google LLC, Mountain View, California).

IRD-information included ocular diagnosis, syndrome, variant gene name(s), left and right eye distance visual acuity, logarithm of the minimum angle of resolution (logMAR) scores for both eyes, and lens status (phakic – no cataract, phakic – cataract, pseudophakic) for both eyes. Referring provider type (ophthalmologist, optometrist, primary care physician, emergency department physician, other) and prior consultation with a low vision specialist were recorded. IRD signs and symptoms included high hyperopia, high myopia, high astigmatism, use of corrective lenses, central or peripheral vision loss, nyctalopia, photophobia, color vision deficits, flashes or floaters, ptosis, cataracts, nystagmus, retinal abnormalities, functional vision loss, strabismus, and amblyopia. High astigmatism was defined as >2.50 diopters; high refractive error was defined as >6.00 diopters.

Additional medical history included obesity, diabetes, cardiac conditions, hearing loss, developmental delay, intellectual disability, neurological conditions, abnormal dentition, prematurity, congenital renal malformations, polydactyly, and syndactyly. Family history variables included IRD diagnosis, nystagmus, high refractive error, nyctalopia, vision loss, color vision deficits, polydactyly, syndactyly, cataracts, strabismus, amblyopia, cardiac conditions, and neurological conditions. The Wisconsin Behavioral Risk Factor Surveillance System (BRFSS) from 2022 was used to serve as a control population for comparison.

Outcomes

The primary outcome was identification of characteristics predictive of age at presentation to the IRD clinic (adult vs pediatric). Secondary outcomes included differences in proximity to the tertiary care center, referring provider type, and diagnoses between pediatric and adult patients.

Statistical Analysis

Fisher exact tests were used to analyze all categorical covariates to determine significant associations between pediatric and adult clinical characteristics. For tables larger than 2x2, the Hommel post-hoc adjustment was applied to correct for multiple comparisons. Significant associations were further quantified by calculating odds ratios and corresponding 95% confidence intervals to provide a more detailed understanding of the relationship within the data.

RESULTS

Patient Characteristics

A total of 538 patients with IRDs were identified, of whom 11 were excluded. Data were collected on 527 patients, including 124 pediatric and 403 adult patients. Patient characteristics are detailed in Table 1.

Characteristics of Presentation to IRD Clinic During Childhood

Among the 124 pediatric patients, the following characteristics were observed: nystagmus (39%), high myopia (24%), high astigmatism (24%), high hyperopia (13%), strabismus (13%), and ptosis (5%) (Table 2). These characteristics differed significantly

from those of adult patients presenting to the clinic for the first time, with statistical significance noted for high hyperopia (P < .001), high myopia (P = .004), high astigmatism (P < .001), ptosis (P = .022), nystagmus (P < .001), and strabismus (P = .001) (Table 2).

Medical characteristics associated with pediatric presentation compared with adult presentation included syndactyly (P = .041), developmental delay (P < .001), and intellectual disability (P < .001) (Table 1). Having a family history of nystagmus (P < .001), high refractive error (P = .002), vision loss (P < .001), strabismus (P = .002), and amblyopia (P = .045) was also associated with pediatric presentation (Table 2).

Among these variables, the strongest associations with pediatric presentation were found for high hyperopia (odds ratio [OR], 49.34; 95% CI, 9.89-1195.80), congenital syndactyly (OR, 9.62; 95% CI, 1.10-227.57), high astigmatism (OR, 6.19; 95% CI, 3.31-11.86), and a history of developmental delay (OR, 6.11; 95% CI, 2.62-15.08) (Supplemental Table 1). Although these findings were statistically significant, their low prevalence limits their generalizability and underscores the need for further studies to validate these associations.

Table 1. Patient Characteristics

	Pediatric (<18 yo) n (%)	Adult (≥18 yo) n (%)	Total n (%)	*P* value	BRFSS Control[a] (≥18 yo) n (%)	BRFSS Control Adult[a] *P* value
N	124	403	527		11276	
Age, n; mean (SD)	9 (5)	49 (17)	39 (22)			
Sex						
Male	79 (64)	212 (53)	291	.04	5338	0.04
Female	45 (36)	190 (47)	235		5938	
NA[b]	1	1	1		0	
Race/ethnicity						
White	86 (84)	325 (93)	411	.30	9749	0.21
Black/African American	10 (10)	18 (5)	28		603	
Asian	3 (3)	6 (2)	9		144	
AI/AN	3 (3)	2 (<1)	5		134	
Other[b]	5	8	10		488	
Declined[b]	0	1	1		NA	
N/A[b]	13	43	63		NA	
Patient drives						
Yes	4 (5)	180 (49)	184	< .001		
No	76 (95)	190 (51)	266			
NA[b]	1	13	14			
Referring provider						
Ophthalmologist	51 (59)	181 (56)	232	.36		
Optometrist	13 (15)	71 (22)	84			
Primary care	22 (26)	72 (22)	94			
Emergency	0 (0)	0 (0)	0			
Other[b]	38	74	112			
Unknown[b]	0	5	5			
Medical characteristics at presentation						
Congenital						
Polydactyly	0 (0)	12 (3)	12 (2)	.078		
Syndactyly	3 (3)	1 (0)	4 (1)	.041		
Kidney malfunction	0 (0)	11 (3)	11 (2)	.076		
Prematurity	14 (12)	30 (8)	44 (9)	.187		
Developmental delay	15 (13)	9 (2)	24 (5)	< .001		
Intellectual disability	16 (14)	17 (4)	33 (6)	< .001		
Abnormal teeth	2 (0)	1 (0)	3 (1)	0.134		
Diabetes	1 (0)	41 (10)	42 (8)	< .001	1506 (10.3)	1
Obesity	9 (8)	77 (20)	86 (17)	.002	3782 (37.7)	< .001
Cardiac condition	7 (6)	100 (26)	107 (20)	< .001	698 (4.6)	< .001
Neurologic condition	19 (16)	75 (19)	94 (18)	.502		
Hearing loss	19 (16)	89 (23)	108 (21)	.125		

Abbreviations: AI/AN, American Indian/Alaska Native; yo, years old; BRFSS, Behavioral Risk Factor Surveillance System; NA, not applicable.

[a]Shows the BRFSS control data from 2022. Control data only included individuals over age 17, thus pediatric comparison was not feasible.

[b]All NA, other, declined, were removed for analyses.

Characteristics of Presentation to IRD Clinic During Adulthood

Among the 403 adult patients, the ocular characteristics most associated with adult presentation included reduced central vision (P = .002), peripheral vision loss (P = .003), color vision deficits (P = .002), nyctalopia (P < .001), flashes/floaters (P < .001), and cataracts (P < .001) compared to pediatric patients (Table 2). Diabetes, obesity, and heart disease were more common in adults than in pediatric patients (P < .001 for all) (Table 1).

Compared to BRFSS control population, obesity (P < .001) and cardiac condition (P < .001) were significantly more prevalent in the adult IRD population, while diabetes was not statistically significant (P = 1.00). Additionally, a family history of cataracts (P = .022) was associated with adult presentation (Table 2).

Proximity to Tertiary Care Center

A smaller proportion of pediatric patients lived less than 20 miles from the tertiary ophthalmology center (13.3%, 95% CI, 8.7-19.7) compared to those living 20 to 80 miles (28.0%, 95% CI 22.0-36.1) and more than 80 miles (28.6%, 95% CI 21.9-35.0) away (Figure 1). There was no significant difference in the proportion of pediatric patients between those living 20 to 80 miles and more than 80 miles from the center (Figure 1).

Referring Provider

There was no significant difference in referring provider type between pediatric and adult patients ($P = .36$) (Table 1). Ophthalmologists accounted for the highest number of referrals in both groups, followed by primary care physicians (Table 1). There was no significant difference in the proportion of pediatric patients referred by any specific clinician type (Supplemental Table 2).

Diagnosis

The most common IRDs among pediatric patients were Leber congenital amaurosis (LCA) and cone-rod dystrophy (Figure 2 and Supplemental Table 3). Other diagnoses, including choroideremia, RP, Stargardt disease, and vitelliform dystrophy, were present at lower proportions in pediatric patients (Figure 2 and Supplemental Table 3). Among adult patients, the most common IRD diagnoses were RP, followed by Stargardt disease (Figure 2).

DISCUSSION

This retrospective cohort study of 527 patients with IRDs identified characteristics most associated with pediatric versus adult presentation to a tertiary care center. Consistent with prior studies,[3-8] our findings confirmed a strong association between high myopia and IRDs, supporting our initial hypothesis. Notably, high hyperopia was significantly associated with pediatric presentation, a finding that is less frequently reported in the literature, although previous studies have noted this association.[2,4,9] Similarly, our results align with prior research demonstrating a strong association between astigmatism and IRD.[6]

Our finding that developmental delay is a predictor of pediatric IRD presentation is consistent with the understanding that children with poor vision may be at increased risk for developmental delays due to limited cues regarding the world around them.[12] Additionally, developmental delay has been reported in certain syndromic IRDs.[13,14] Anatomic variants such as polydactyly, brachydactyly, and syndactyly have also been described in patients with IRDs[15] which supports our finding that syndactyly was more commonly associated with pediatric presentation compared to adult presentation.

High proportions of pediatric and adult patients presented with reduced central vision (33%), color vision deficits (34%), nyctalopia (37%), and photophobia (53%), with no significant differences between the groups.

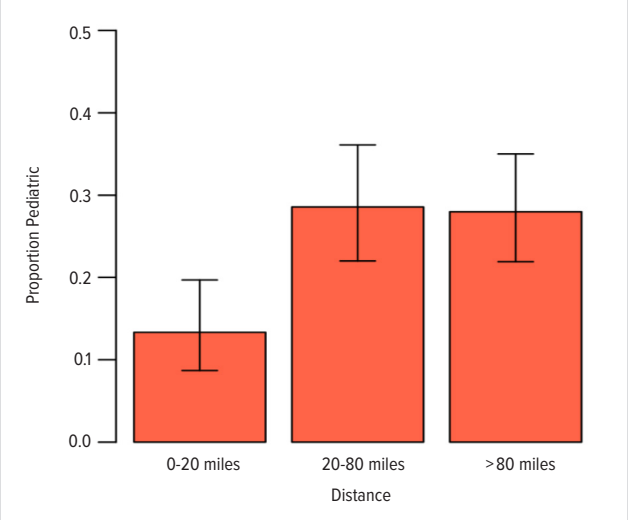
In adults, the characteristics most associated with IRD presentation included flashes/floaters, reduced central vision, peripheral vision loss, cataracts, diabetes, obesity, cardiac conditions, and a family history of cataracts. Previous research has linked syndromic IRDs with diabetes, obesity, and cardiac conditions.[16] In our study, cardiac conditions were more prevalent in the adult IRD population compared to the control group. Obesity was significantly less prevalent, and diabetes prevalence was similar between the IRD adult population and the control group.

Table 2. Patient Ocular Characteristics and Family History at Presentation

	Pediatric n (%)	Adult n (%)	Total N (%)	*P* value
Ocular characteristics				
High hyperopia	16 (13)	1 (0)	17 (3)	<.001
High myopia	29 (24)	47 (12)	76 (15)	.004
High astigmatism	29 (24)	18 (5)	47 (9)	<.001
Wears correction	81 (70)	299 (75)	380 (73)	.078
Reduced central vision	36 (33)	196 (50)	232 (46)	.002
Peripheral vision loss	27 (25)	158 (40)	185 (37)	.003
Color vision deficits	37 (34)	197 (50)	234 (47)	.002
Functional vision loss	0 (0)	0 (0)	0 (0)	1
Nyctalopia	41 (37)	256 (65)	297 (59)	<.001
Photophobia	63 (53)	240 (61)	303 (59)	.138
Flashes/floaters	21 (19)	257 (66)	278 (56)	<.001
Cataracts	7 (6)	212 (53)	219 (42)	<.001
Ptosis	6 (5)	5 (1)	11 (2)	.022
Nystagmus	47 (39)	43 (11)	90 (17)	<.001
Retinal abnormalities	117 (98)	394 (99)	511 (99)	.141
Both eyes affected	120 (99)	391 (99)	511 (99)	1
Strabismus	16 (13)	17 (4)	33 (6)	.001
Amblyopia	11 (9)	18 (5)	29 (5)	.077
Family history				
Diagnosed IRD	33 (27)	137 (35)	170 (33)	.151
Nystagmus	13 (11)	10 (3)	23 (5)	<.001
High refractive error	8 (7)	4 (1)	12 (2)	.002
Nyctalopia	16 (13)	35 (9)	51 (10)	.224
Vision loss	50 (75)	167 (43)	217 (42)	<.001
Color vision deficit	11 (9)	27 (7)	38 (7)	.432
Polydactyly/syndactyly	1 (0)	6 (2)	7 (1)	1
Cataract	20 (16)	105 (27)	125 (24)	.022
Strabismus	28 (24)	46 (12)	74 (14)	.002
Amblyopia	17 (15)	31 (8)	48 (9)	.045
Cardiac condition	9 (8)	46 (12)	55 (11)	.239
Neurological condition	15 (12)	63 (16)	77 (15)	.317

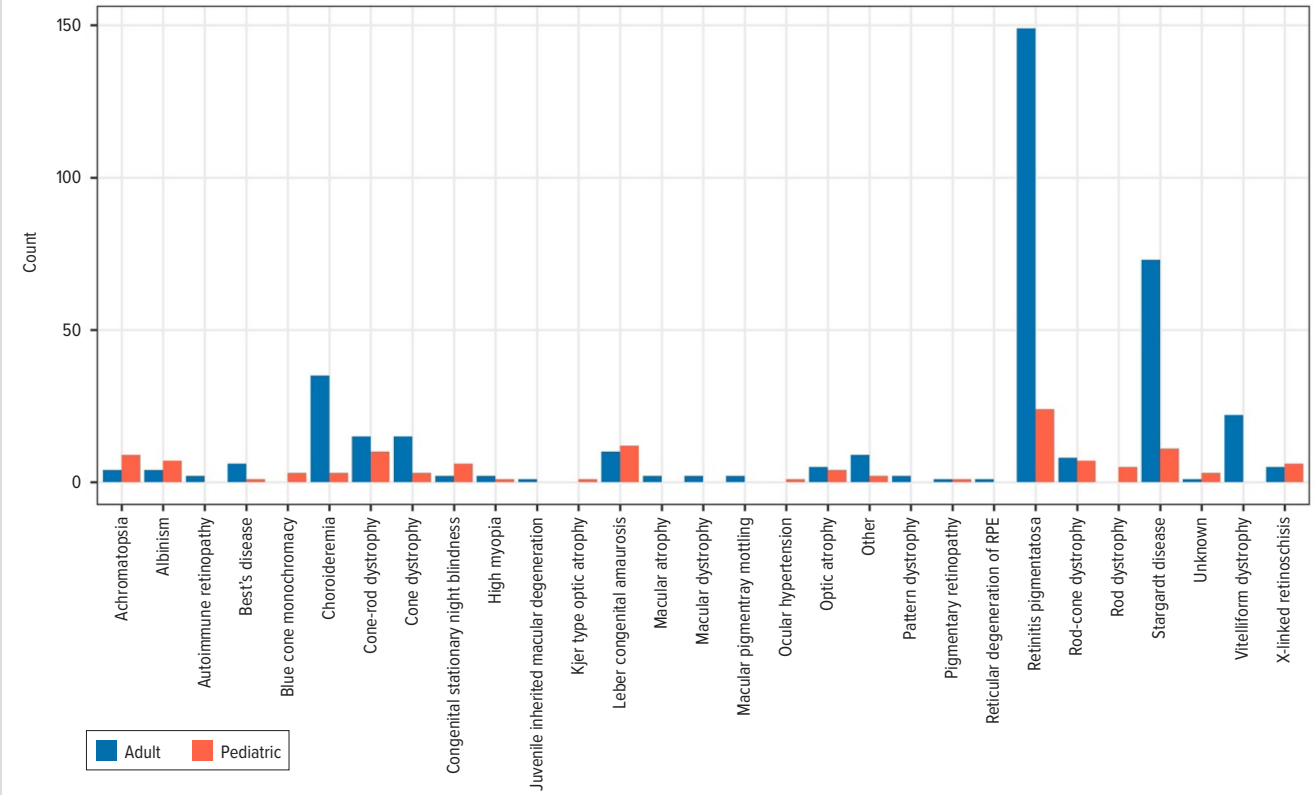
Abbreviation: IRD, Inherited retinal degenerations.
Pediatric: <18 years old; adult ≥18 years old.

Figure 1. Proportion of Pediatric IRD Patients by Distance From Tertiary Care Center



Error bars indicate 95% CIs. Distances are categorized as <20 miles, 20–80 miles, and >80 miles.

Figure 2. Counts of Pediatric and Adult IRD Patients by Ocular Diagnosis at Initial Presentation



In a large study of patients with RP, 170 individuals reported light flashes as a common problem,[17] which is consistent with our findings. The predictors of reduced central and peripheral vision align with previous literature describing patients with RP becoming legally blind by age 40 due to severely reduced visual fields and experiencing central visual loss by age 60.[18] Our finding that cataracts are associated with adult presentation is also supported by prior studies. Based on absolute counts, RP was the most common diagnosis, and RP has previously been linked to cataract development. In a study by Fishman et al, half of the sample of RP patients were found to have cataracts.[5] We also found that a family history of cataracts was associated with adult presentation, which may reflect both the genetic basis of IRDs and the higher prevalence of cataracts in the general adult population.

Compared to pediatric patients, adults presented with more medical comorbidities, including diabetes, obesity, and cardiac conditions. These differences may reflect the type of systemic diseases that typically present during childhood versus adulthood. It is also possible that adult patients were more likely to regularly receive health care, increasing the likelihood of comorbidity diagnosis. This study contributes to our understanding of predictors of pediatric versus adult presentation of IRDs.

Contrary to our hypothesis that closer proximity to a tertiary care center would result in more pediatric referrals, we found the opposite. A smaller proportion of pediatric patients lived less than 20 miles from the center compared to those living farther away. Pediatric patients were more likely to originate from 20 miles away or more. Access to a tertiary care center did not correlate with increased pediatric referrals, suggesting that other factors may influence this finding. Parents may be more willing to travel longer distances for their children, or transportation barriers may affect access. Another possibility is that comprehensive ophthalmologists may feel more comfortable managing adult IRD patients, while fewer may be equipped to care for pediatric patients. Additionally, the shortage of pediatric ophthalmologists and the challenges of examining children may contribute to this finding.

Regarding type of referring provider, no significant difference was found between pediatric and adult patients. Based on raw data, ophthalmologists accounted for the highest number of referrals, followed by primary care physicians. This may reflect the role of primary care physicians as initial points of contact and the specialized training of ophthalmologists in recognizing IRD signs. Given that non-eye care professionals comprised a substantial portion of referrals, it is important to educate clinicians on symptoms that warrant referral for IRD evaluation.

The diagnoses most prevalent in pediatric versus adult patients in this study reflect current knowledge regarding age of

onset of IRDs.[19,20] For example, we found a higher proportion of pediatric patients diagnosed with LCA, and a greater number of vitelliform maculopathy diagnoses in adults. The larger number of RP diagnoses in adults is consistent with RP being the most common IRD, with an estimated prevalence of 1 in 4000 individuals.[21] Our sample reflects these prevalence patterns across age groups.

Limitations of this study include its single-site design and the absence of a pediatric control population for comparison. Despite these limitations, the study included a large sample size of 527 patients with extensive data points, which is notable given the low prevalence of IRDs in the population. Another consideration is that the majority of the patients were White, likely reflecting the local demographics of the tertiary care center, which limited our abilility to examine racial disparities.

CONCLUSIONS

We identified characteristics associated with pediatric and adult presentation in patients with IRDs, thereby addressing current knowledge gaps. Recognizing these characteristics is essential to initiate treatment early and reduce vision loss. A better understanding of these characteristics may facilitate earlier recognition, improve education for clinicians most likely to encounter IRDs, and support timely treatment.

Proximity to a tertiary care center was not the primary factor influencing age at presentation. Further research is needed to explore barriers faced by patients living farther from specialty centers and to develop outreach strategies that promote early recognition and referral. Additionally, exploration of genetic patterns across different regions and communities remains an important area for future study.

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