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Frequency and distribution of ophthalmic surgical procedures among patients with inherited retinal diseases

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Abstract

Objective or Purpose: In this study, we aimed to characterize the frequency and distribution of ocular surgeries in patients with inherited retinal diseases (IRDs) and evaluate associated patient and disease factors.

Design: Retrospective cohort.

Participants: Subjects 18 years and older who were followed at the Johns Hopkins Genetic Eye Disease (GEDi) Center and had undergone an ophthalmic surgical or laser procedure.

Methods: We studied a retrospective cohort of patients with an IRD diagnosis to analyze the occurrence of laser and incisional surgeries. Subjects were categorized into two groups: central dysfunction (macular/cone/cone-rod dystrophy, “MCCRD group”) and panretinal or peripheral dysfunction (retinitis pigmentosa-like, “RP group”). Genetic testing status was recorded. The association of patient and disease factors on the frequency, distribution, and timing of surgeries was analyzed.

Main outcome Measure: Prevalence, prevalence odds ratio (POR), hazard ratio (HR) of ophthalmic procedures by phenotype.

Results: A total of 1472 eyes of 736 subjects were evaluated. Among them, 31.3% (n = 230) had undergone ocular surgery, and 78.3% of those (n=180/230) had a history of more than one surgery. A total of 602 surgical procedures were analyzed. Cataract extraction with intraocular lens implantation (CEIOL) was the most common (51.2%), followed by YAG capsulotomy, refractive surgery, retinal surgery, and others. CEIOL occurred more frequently in RP than in MCCRD

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subjects (POR 2.59, p = 0.002). RP subjects underwent CEIOL at a younger age than MCCRD patients (HR = 2.11, p < 0.001).

Conclusion: Approximately one-third of IRD patients had a history of laser or incisional surgery. CEIOL was the most common surgery; its frequency and timing may be associated with IRD phenotype. This data may inform the design of prospective research. Such efforts may illuminate routine clinical decision-making and contribute to surgical strategy development for cell and gene therapy delivery.

Introduction

Inherited retinal dystrophies (IRD) are a group of genetically and phenotypically heterogeneous diseases that typically lead to vision loss due to progressive retinal degeneration.[1] IRDs were considered incurable at the molecular level until the approval of voretigene neparvovec-rzyl, the gene augmentation treatment for biallelic *RPE65*-associated IRD.[2] Given the general lack of disease-modifying IRD treatments, treating ocular comorbidities to improve or preserve visual function is a critical component of the clinical care of IRD patients. While optical or pharmacologic treatment can be used for refractive error and cystoid macular edema,[3,4] laser or incisional surgery is usually required for cataracts, posterior capsule opacity, macular hole, severe glaucoma, and strabismus, among other conditions, in IRD patients.[5-9]

The most well-studied standard-care surgical treatment in IRD is cataract extraction with intraocular lens implantation (CEIOL).[9-11] Other surgical treatments in the setting of concomitant IRD include epiretinal membrane (ERM) removal,[12,13] full-thickness macular hole (FTMH) repair,[14,15] strabismus correction,[16,17] and refractive surgery.[18] It is known that there is a high risk of post-CEIOL posterior capsular opacification and cystoid macular edema in IRD patients.[19,20] Those observations suggest that IRD eyes respond to surgery in unique ways that are poorly understood at present. Therefore, it is plausible that other surgical procedures (such as vitrectomy, trabeculectomy, and strabismus surgery) may also pose unique or particularly severe risks in IRD patients. However, because the evidence base regarding standard-care surgical outcomes in IRD cases is relatively weak, physicians lack data to make clinical decisions and to guide the informed consent process. This knowledge gap is particularly troubling because surgical procedures are likely to become more common in IRD patients with the advent of cell and gene therapy. The increasing implementation of genetic testing provides an opportunity to study genotype-specific prospective outcomes of ocular surgery.[9,11,13,21]

To facilitate the rational design of a prospective study on standard-care ocular surgery in IRD patients, estimates of the prevalence, indications, and types of ocular surgery in this population are needed. This information will enable the most frequent surgeries to be prioritized for further research. Here, we aimed to characterize the frequency and distribution of ocular surgeries in a retrospective IRD cohort. We also aimed to understand how the frequency and distribution of ocular surgeries were influenced by IRD phenotype, IRD genotype, sex, and age.

Methods

This project was approved by the Johns Hopkins School of Medicine Institutional Review Board (ID: IRB00213488) and conformed to the tenets of the Declaration of Helsinki. Informed consent was waived as the study was conducted retrospectively. Electronic medical records (EMRs) of all patients seen in the IRD clinic at the Genetic Eye Diseases Center of the Wilmer Eye Institute, Johns Hopkins Hospital, from 2014 to 2020 were screened for inclusion. Subjects were selected based on an established clinical diagnosis of IRD. Subjects were grouped according to published IRD classifications into: 1. IRD predominantly or initially affecting the central retina or cone photoreceptors, termed macular/cone/cone-rod dystrophy (hereafter referred to as the "MCCRD group") and, 2. IRD initially affects the peripheral retina or rod photoreceptors, termed retinitis pigmentosa (RP)-spectrum (hereafter referred to as the "RP group").[22-24] The latter group included IRD cases with very advanced panretinal degeneration in which cone versus rod predominance could not be ascertained phenotypically, genetically, or by symptoms. For this study, we defined surgical procedures to include all laser and incisional procedures to ensure broad data capture.

Patients were classified as genetically confirmed (gene+) if a pathogenic or likely pathogenic variant consistent with their phenotype was found. Inheritance patterns were recorded based on the gene involved and/or pedigree information. Patients were classified as genetically unconfirmed (gene−) if a robust IRD genetic panel was negative or inconclusive (panels were considered robust if covering more than 250 genes). Patients without genetic testing or who had received a negative or inconclusive result on a panel of less than 250 genes were classified as untested.

Ocular surgical history was extracted from the EMRs by searching with the phrase: "surg OR iol OR vitrectomy OR yag OR laser OR strabismus OR lasik OR lasek OR prk OR iridotomy OR blepharoplasty OR operative OR phaco OR ppv OR rectus OR trabec OR bleb OR tube OR gdi OR ectropion OR entropion OR pseudophakia OR ceiol OR pciol." Where available, PDF files in each EMR were manually searched for surgical history.

Biostatistical analysis.

Statistical analysis was performed using R Version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). All p values in this study were two-sided with a statistical significance level of 0.05. Continuous variables were summarized as mean with standard deviation and categorical variables were presented as the frequency with proportion. The summary distribution of duration (in years from birth) to CEIOL was estimated using the Kaplan-Meier method. A marginal Cox proportional hazard model was used to compare duration to CEIOL by phenotypic grouping (RP vs. MCCRD), sex, and groups of eyes. 95% confidence intervals (CI) for estimated hazard ratios (HR) were calculated using a robust sandwich variance estimate to adjust for between-eye correlation. The survival analysis was conducted using the "coxph" function specified with the "cluster" option in the "survival" function from R. The association of surgical prevalence and some factors, including phenotype, sex, and genetic status, were analyzed by generalized estimation equation (GEE) logistic regression for all the eyes to account for the between-eye correlation and logistic regression for single eye groups (OD and OS). Among the study's top five most

common surgical categories, the prevalence odds ratio (POR) for each surgery comparing RP to MCCRD was summarized for all eyes and single-eye groups. Among the top two most common surgical categories, POR for each surgery comparing male to female was summarized separately in RP and MCCRD groups for all eyes and single eye groups. In addition, POR for CEIOL comparing gene+, gene−, and untested groups was presented separately in RP and MCCRD groups for all eyes and single-eye groups. All POR with 95% CI and p values were displayed in forest plots.

Results

A total of 1472 eyes of 736 subjects were included (Supplementary Table 1). The subjects were classified as the RP group, n=354, and the MCCRD group, n=382. At the time of data analysis, the average age of subjects was 51.5 ± 19.5 years, and 52.7% were female. Table S2 shows the diagnoses included in the RP and MCCRRD groups. The proportion of cases with a positive genetic result was 37.8%, whereas 27.9% had negative or inconclusive testing, and 34.4% had not been genetically tested.

Frequency and distribution of ocular surgery in the cohort

We quantified the frequency of surgeries from both the per-eye and per-subject perspectives. From the per-subject perspective, the frequency of subjects who underwent ocular surgery was 31.3% (230 of 736 subjects). From the per-eye perspective, a total of 410 eyes, including 203 right eyes (OD) and 207 left eyes (OS), had at least one surgery (Supplementary Table 3). Therefore, the frequency of eyes that underwent any ocular surgery was 27.9% (410 of 1472 eyes). A total of 133 eyes had a history of more than one procedure; this number comprised 9.0% of all eyes and 32.4% of eyes with a history of any procedure.

There was a total of 602 surgeries in the cohort. Surgeries were categorized into groups, as shown in **Supplementary Table 4**. The frequency of each surgery by surgical category and ocular laterality is summarized in Table 3. Among all surgeries, CEIOL made up the majority of surgeries (51.2%). Most eyes (154 OD, 154 OS) had undergone CEIOL. The second most common procedure was YAG capsulotomy (42 OD, 39 OS). Refractive surgery ranked as the third most common procedure (23 OD, 23 OS). Among these cases, the majority underwent laser-assisted in situ keratomileusis (LASIK), with 19 bilateral procedures. Additionally, one case involved photorefractive keratectomy, and another case featured the placement of Intacts contacts. Data on the type of surgery was unavailable for two cases.

Of subjects who underwent any ocular surgery, 78.3% (180 of 230) had a history of surgery in both eyes. CEIOL was the most common bilateral procedure (18.3% of all subjects). Smaller proportions of subjects had a history of bilaterally concordant surgeries in other categories (e.g., bilateral retinal surgery) (Table 5), and the remainder had bilateral surgeries from more than one category.

Influence of IRD phenotype and genotype, and subject sex and age, on ocular surgery

The CEIOL prevalence odds ratio (POR) for RP: MCCRD was 2.59, p = 0.002 for all subjects, 2.42, p = 0.008 for OD eyes and 2.84, p = 0.001 for OS eyes. These data indicate that CEIOL was more common in RP subjects than MCCRD subjects (Figure 1).

The refractive surgery prevalence odds ratio for RP:MCCRD was 0.4, p = 0.04 for all subjects, 0.4, p = 0.04 for OD, and 0.4, p = 0.04 for OS. The retinal surgery POR for RP:MCCRD was 0.47, p = 0.04 for all subjects, 0.54, p = 0.16 for OD, and 0.42, p = 0.08 for OS. These data indicate that refractive surgery and retinal surgery were more common in MCCRD than in RP. No significant difference was found in the relative frequency of YAG capsulotomy and glaucoma surgery between RP and MCCRD (Figure 1).

There was no significant difference between gene+, gene−, and untested subjects in the prevalence odds for CEIOL (data not shown). Other surgical categories lacked sufficient gene− subjects for valid comparisons. There was no significant difference between surgical prevalence odds between male and female subjects for the two most common surgeries in our cohort, CEIOL and YAG capsulotomy (data not shown).

RP subjects underwent CEIOL at a younger age than MCCRD subjects (HR = 2.11, p < 0.001; Figure 2A). There was no significant difference in age at the first or only CEIOL by sex (HR = 1.07, p = 0.67; Figure 2B) or laterality (HR = 0.91, p = 0.05; Figure 2C). The age at first or only CEIOL did not differ based on genetic testing status in RP patients (gene− vs. untested HR = 1.13, p = 0.51; gene+ vs. untested HR = 1.10, p = 0.58; Figure 3A) or MCCRD patients (gene− vs. untested HR = 1.29, p = 0.35; gene+ vs. untested HR = 1.42, p = 0.24; Figure 3B). An additional analysis was conducted, whereby patients with gene− and untested statuses were grouped together. However, no significant differences were identified in the age at first or only CEIOL based on genetic status in RP patients (gene+ vs. gene−/untested, HR 1.4, p= 0.79) (Figure 3C) or MCCRD patients (HR 1.34, p=0.31) (Figure 3D).

Discussion

The data show that ocular surgery in subjects with IRD is relatively common, and various procedures can occur in this population. Ocular surgery occurred with a frequency of approximately 1:3 when considered from the per-subject and per-eye perspectives. Approximately one in three eyes underwent multiple procedures. Among IRD patients who underwent surgery, over two-thirds had a history of surgery in both eyes.

Among the more than 600 surgical procedures sampled in this dataset, cataract surgery was the most common, accounting for about half of all surgeries, followed by YAG capsulotomy and refractive surgery. Surprisingly, other surgical procedures were the most common among the next tier, with an approximate frequency of 5–10%. Other procedures in this tier included vitreoretinal, refractive, glaucoma, and strabismus procedures. Surgeries in the third tier with <5% frequency in this dataset and included eyelid surgery, other CEIOL procedures (such as IOL exchange), corneal transplantation, and others. The frequency of certain surgeries appeared to be associated with the IRD phenotype category in terms of a

simple and approximate classification of central (MCCRD) versus peripheral (RP) retinal damage predominance. Broadly, the data underscore the need for future research on this topic to address a broad range of surgeries and consider potentially important variables, including age, sex, and IRD characteristics.

In our sample, CEIOL was by far the most common surgery, making up 51.2% of total surgeries. Most publications on surgery in the IRD population focus on CEIOL. In general, IRD patients experience an improvement in best-corrected visual acuity following CEIOL.[9-11,25] While reports of severe complications are rare,[26] IRD patients appear to be at higher risk for cystoid macular edema (CME) and posterior capsular opacification (PCO). [19] The reported prevalence of CME range from 0-13% [11,19] compared to 0.1 - 2.4% in the general population. [27] PCO is particularly common among IRD patients following CEIOL, with prevalence reported up to 83%,[28] well above what is commonly reported in the general population. [29,30]

On average, subjects with RP underwent CEIOL more frequently and at an earlier age than MCCRD subjects. This could be explained by the relatively early and common onset of cataracts in RP, as cataract is the most commonly seen anterior segment comorbidity, usually occurring between 20-40 years old. [31] An alternative or additional explanation is that MCCRD patients may frequently encounter recommendations to defer cataract surgery owing to the presence of macula or fovea damage that lessens the expectation of visual benefit from CEIOL. In comparison with the general population in the United States and the patients followed at this center, IRD patients in our cohort underwent CEIOL at younger ages (67.7 vs. 67.2 vs. 59.8, respectively). [32,33]

We detected cases that underwent refractive procedures, even in those with MCCRD. While RP patients have been found to have a higher prevalence of refractive error compared to the general population,[34] cone-dominated retinal dystrophies have been shown to be up to twice as likely to lead to refractive error.[35] While refractive surgery may enhance vision-related quality of life in some IRD cases, it is unclear whether these procedures confer sustained or long-term benefits, and further research may help to clarify which IRD patients, if any, are likely to benefit from this treatment. We also found that retinal surgery was more common in MCCRD cases. Within Stargardt disease (the most common MCCRD subtype in our series), vitreoretinal interface abnormalities may predispose to macular hole formation and epiretinal membrane formation. [14,36] Although retinal procedures were less prevalent in patients with panretinal phenotypes, it's noteworthy that symptomatic schisis-related retinal detachment is a recognized complication in individuals with retinoschisis.[37] This condition may necessitate interventions such as retinopexy, pars plana vitrectomy, and/or scleral buckle. In contrast, retinal detachment is less frequently observed in patients with RP (0.7% to 1.3%), with most pathological breaks occurring within the area of bony spicules.[38,39] Notably, the reattachment rates among this group are generally high, ranging from 91% to 95%.[39] Our data support a need to study the risks of standard-care vitreoretinal procedures in IRD cases, especially macular dystrophies.

Interestingly, our study did not reveal any differences in surgical prevalence based on sex, perhaps because of limited cohort size. Previous studies in the general population

have shown a male predominance in CEIOL and vitrectomy prevalence, while YAG capsulotomy appears more frequent in females. [40-42] Previous studies have revealed phenotypic differences in IRD patients with genetic confirmation compared to those without. [43] In the present study, we observed no difference in surgery prevalence or age to CEIOL based on genetic confirmation status. Building on a prior investigation that demonstrated significantly higher visual field index and mean central retinal layer in patients with unresolved RP compared to resolved RP cases,[44] we performed an additional analysis by grouping patients with gene− and untested statuses. Still, no discernible differences were detected between the groups.

This study has several limitations, the most important of which is that this is a single-center retrospective study. Some of the less common surgeries were too few to allow meaningful comparisons between groups or to further categorize patients by gene or specific IRD. We did not analyze any outcome variables, as that question was beyond the scope and design of this study. In addition, we acknowledge the potential presence of referral bias in this population due to our center's specialized nature, which serves a vast referral network. For example, our cohort may skew toward cases of greater complexity, such as those with systemic manifestations and other ocular comorbidities, including cataracts, uveitis, and optic neuropathy. Consequently, this may result in a study population not representative of patients with IRD at other clinics or healthcare settings.

Because of sample size limitations, the patients were grouped into 2 categories. However, we acknowledge the limitations and the absence of standardized definitions for grouping patients into RP and MCCRD groups. Establishing standardized nomenclature would enhance future prospective studies. Furthermore, the study did not evaluate intravitreal injections. Given the association of certain IRDs with macular neovascularization, future studies could include intravitreal injections within this population. Still, our data will contribute to laying the ground for prospective studies on short- and long-term outcomes of various ocular surgeries. Still, our data will contribute to laying the ground for prospective studies on short- and long-term outcomes of various ocular surgeries.

In conclusion, approximately one-third of IRD patients experience ocular surgery, spanning a broad range of procedures and indications. CEIOL was the most common surgery in IRD patients, and it occurred earlier and more frequently in RP than in MCCRD. Refractive and retinal surgery occurred more regularly in MCCRD than in RP cases. As ocular surgery for routine indications plays an important role in preserving or improving vision in people with IRD, prospective surgical outcomes research in IRD eyes is warranted. A better evidence base regarding surgical outcomes in IRD will likely illuminate clinical decision-making and potentially inform surgical strategy development for retinal cell and gene therapy delivery approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

RP	Retinitis pigmentosa
MCCRD	Macular/cone/cone-rod dystrophy
CEIOL	Cataract extraction and intraocular lens implantation
YAG laser	Yttrium aluminum garnet laser
IRD	Inherited retinal disease
ERM	Epiretinal membrane
FTMH	Full-thickness macular hole
GEE	Generalized estimation equation
POR	Prevalence odds ratio
HR	Hazard ratio
OD	right eye
OS	left eye

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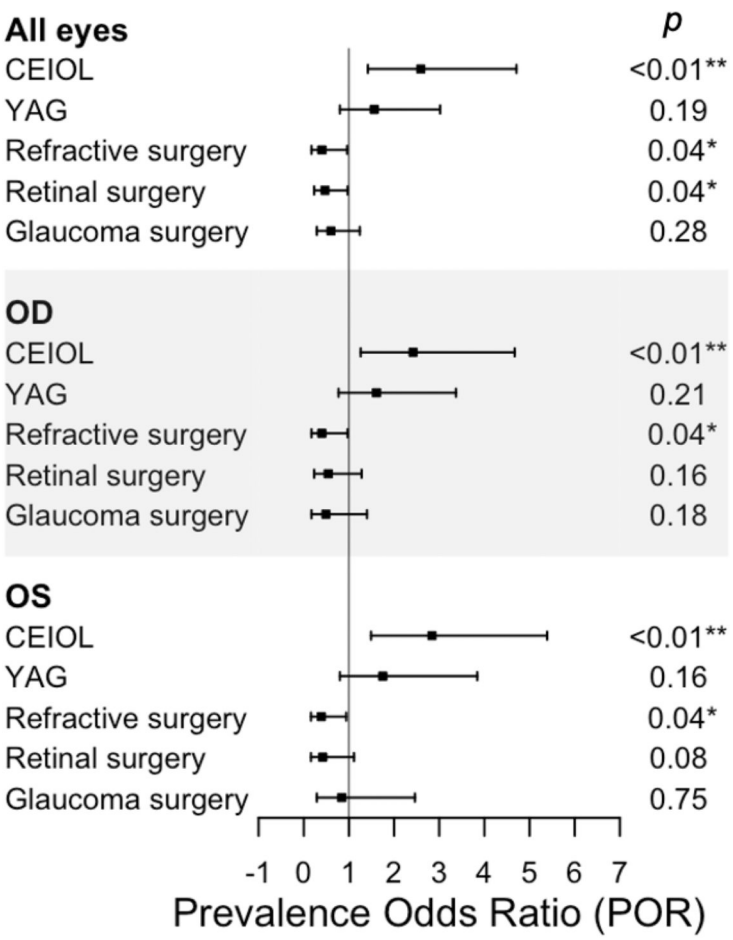

Figure 1. Surgical prevalence by phenotype.

Prevalence odds ratios are shown comparing Retinitis Pigmentosa: Macular/Cone/Cone-rod Dystrophy for the five most common surgical categories in the current dataset. Data are presented as prevalence odds ratio Retinitis Pigmentosa: Macular/Cone/Cone-rod Dystrophy with 95% confidence interval. Prevalence odds ratios > 1 indicate a greater prevalence of cases in the Retinitis Pigmentosa group than in the Macular/Cone/Cone-rod Dystrophy group. *$p < 0.05$, **$p < 0.01$

Abbreviations: OD: right eye; OS: left eye; CEIOL: Cataract extraction and intraocular lens; RP: retinitis pigmentosa; MCCRD: macular/cone/cone-rod dystrophy.

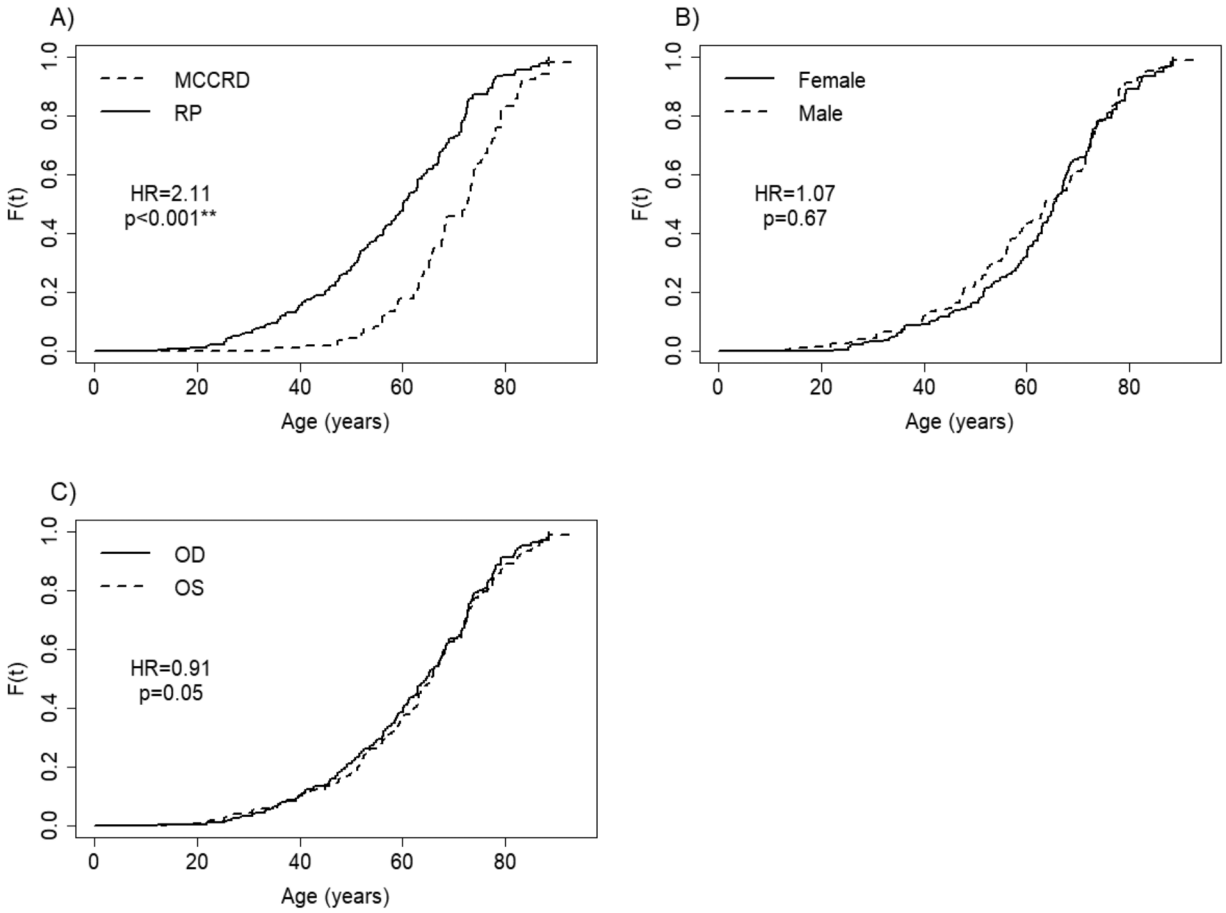

Figure 2. Age at the first or only Cataract extraction and intraocular lens procedure by phenotypic group, sex, and eye.

Cumulative incidence curves show the remaining proportion of patients without surgery (F(t)) who will eventually undergo cataract extraction and intraocular lens. A: Macular/Cone/Cone-rod Dystrophy patients underwent Cataract extraction and intraocular lens at a significantly older age compared to Retinitis Pigmentosa cases, Hazard Ratio (HR) 2.11, $p < 0.001$. B: There was no significant difference in age to the first or only Cataract extraction and intraocular lens between males and females, hazard ratio = 1.07, $p = 0.67$. C: There was no significant difference in age to first or only CEIOL between OD and OS eyes, HR = 0.91, $p = 0.05$.

Abbreviations: OD: right eye; OS: left eye; CEIOL: Cataract extraction and intraocular lens; HR: hazard ratio; RP: retinitis pigmentosa; MCCRD: macular/cone/cone-rod dystrophy.

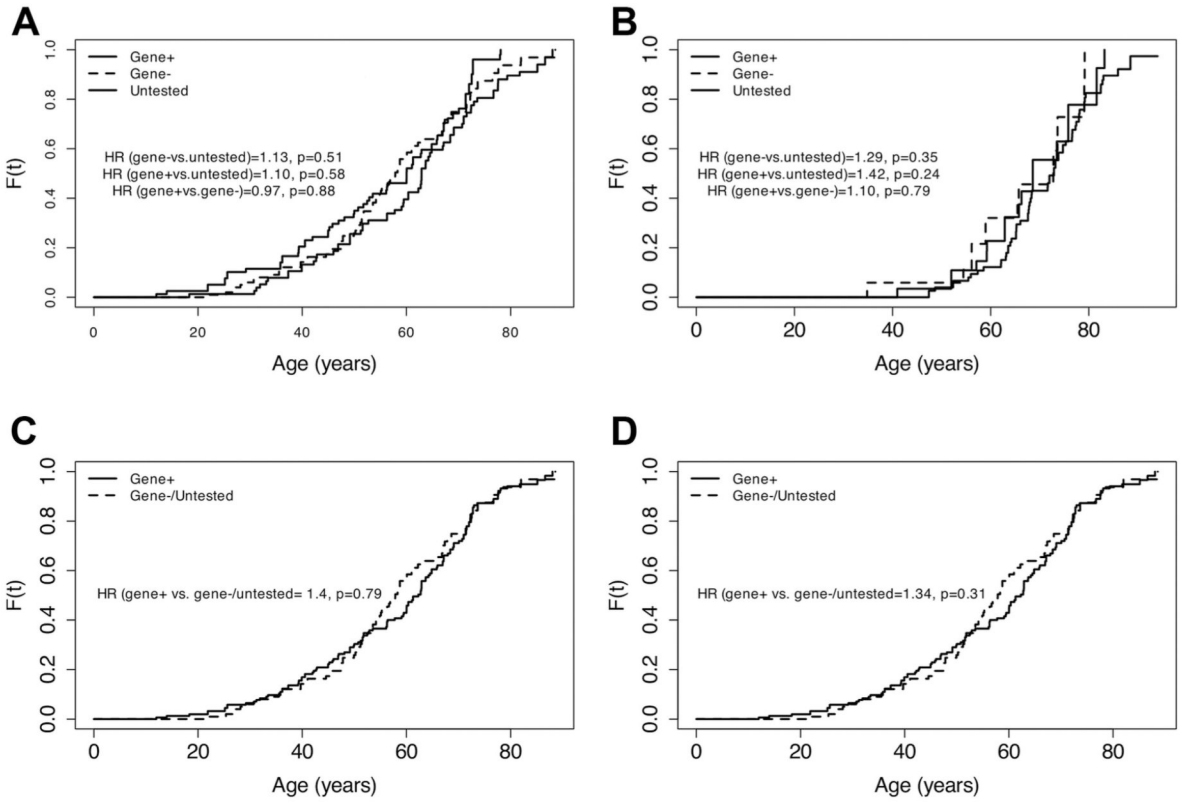

Figure 3. Age to first Cataract extraction and intraocular lens by genetic status,

Cumulative incidence curves show the remaining proportion of patients without surgery (F(t)) who will eventually undergo cataract extraction and intraocular lens. A: Among Retinitis Pigmentosa patients, there was no significant difference in age to first Cataract extraction and intraocular lens between gene− and untested, HR = 1.13, p = 0.51 or gene+ vs untested, HR = 1.10, p = 0.58. B: Among Macular/Cone/Cone-rod Dystrophy patients, there was no significant difference in age to first Cataract extraction and intraocular lens between gene− vs. untested, HR = 1.29, p = 0.35 or gene+ vs untested, HR = 1.42, p = 0.24. C: Among Retinitis Pigmentosa patients, there was no significant difference in age to first Cataract extraction and intraocular lens between gene+ and gene−/untested, HR =1.4, p = 0.79. D: Among Macular/Cone/Cone-rod Dystrophy patients, there was no significant difference in age to first Cataract extraction and intraocular lens between gene+ vs gene−/untested, HR = 1.34, p = 0.31.

Abbreviations: HR: hazard ratio; RP: retinitis pigmentosa; MCCRD: macular/cone/cone-rod dystrophy.

Table 3.

Distribution of surgical categories.

Data presented as n (% of total number of surgeries). Abbreviations: OD: right eye; OS: left eye; CEIOL: Cataract extraction and intraocular lens. There were 180 subjects with bilateral surgery.

Surgical category	OD (n=203)	OS (n=207)	Sum (n=410)	Bilateral cases
CEIOL	154 (50.3)	154 (52.0)	308 (51.2)	135 (61.4)
YAG capsulotomy	42 (13.7)	39 (13.2)	81 (13.4)	23 (10.5)
Refractive surgery	23 (7.5)	23 (7.8)	46 (7.6)	23 (10.5)
Retinal surgery	32 (10.5)	23 (7.8)	55 (9.1)	7 (3.2)
Glaucoma surgery	16 (5.2)	18 (6.1)	34 (5.6)	10 (4.5)
Strabismus	16 (5.2)	17 (5.7)	33 (5.5)	11 (5.0)
Lid surgery	12 (3.9)	15 (5.1)	27 (4.5)	11 (5.0)
CEIOL related procedures	9 (2.9)	2 (0.7)	11 (1.8)	0 (0)
Corneal transplant	0 (0)	4 (1.4)	4 (0.6)	0 (0)
Other	2 (0.7)	1 (0.3)	3 (0.5)	0 (0)
Total number of surgeries	**306**	**296**	**602**	**220**

Table 5.

Distribution of subjects with bilaterally concordant surgical category

Abbreviations: CEIOL: cataract extraction and intraocular lens

Surgical category	Portion of subjects (%) with bilaterally concordant surgical category
CEIOL	18.3
YAG capsulotomy	3.1
Refractive surgery	3.1
Retinal surgery	1.0
Glaucoma surgery	1.4
Strabismus	1.5
Lid surgery	1.5
CEIOL related procedures	0
Corneal transplant	0
Other	0
Total	30%