*Precis / Highlights

Female carriers of X-linked retinitis pigmentosa are sometimes symptomatic. We describe the incidence and severity of visual loss in 242 carriers, including 121 with known mutations. 2% of carriers were legally blind from decreased visual acuity.

Visual Function in Carriers of X-linked Retinitis Pigmentosa

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Abstract

Purpose: To determine the frequency and severity of visual function loss in female carriers of X-linked retinitis pigmentosa (XLRP).

Design: Case series.

Participants: XLRP carriers with cross-sectional data (n = 242) and longitudinal data (n = 34, median follow-up: 16 years, follow-up range: 3-37 years). Half of the carriers were from *RPGR*- or *RP2*-genotyped families.

Methods: Retrospective medical records review.

Main Outcome Measures: Visual acuities, visual field areas, final dark adaptation thresholds, and full-field ERGs to 0.5 Hz and 30 Hz flashes.

Results: In genotyped families, 40% of carriers showed a baseline abnormality on at least one of the three psychophysical tests. There was a wide range of function among carriers; for example 3 of 121 (2%) of genotyped carriers were legally blind due to poor visual acuity, some as young as 35 years of age. Visual fields were less affected than visual acuity. In all carriers, the average ERG amplitude to 30 Hz flashes was about 50% of normal, and the average exponential rate of amplitude loss over time was half that of XLRP males (3.7%/year vs 7.4%/year, respectively). Among obligate carriers with affected fathers and/or sons, 53 of 55 (96%) had abnormal baseline ERGs. Some carriers who initially had completely normal fundi in both eyes went on to develop moderately decreased vision, though not legal blindness. Among carriers with *RPGR* mutations, those with mutations in ORF15, compared to those in exons 1-14, had worse final dark adaptation thresholds and lower 0.5 Hz and 30 Hz ERG amplitudes.

Conclusions: Most carriers of XLRP had mildly or moderately reduced visual function but rarely became legally blind. In most cases, obligate carriers could be identified by ERG testing. Carriers of *RPGR* ORF15 mutations tended to have worse visual function than carriers of *RPGR* exon 1-14 mutations. Since XLRP carrier ERG amplitudes and decay rates over time were on average half of those of affected males, these observations were consistent with the Lyon hypothesis of random X-inactivation.

Introduction

It has long been appreciated that female carriers of X-linked retinitis pigmentosa (XLRP) are sometimes symptomatic.[1,2] Profoundly affected XLRP carriers were reported by McKenzie in 1951.[3] Although he described a family with 8 carrier females who passed the disease to their sons without experiencing any visual symptoms, the pedigree also contained two women who went blind in their 80's due to retinal degeneration and two younger women with mild symptoms. Since that time this general observation has been confirmed — with many XLRP carriers retaining useful vision and others becoming severely affected.[1,2,4-13] A published case series of 27 carriers reported that carriers with pigmentary changes had a poorer visual prognosis than carriers with a normal fundus appearance[6]; furthermore, none of 11 patients with a normal fundus or only a tapetal-like reflex had any significant change in visual acuity or visual field area over time.[6] In a study describing a large kindred with an *RPGR* mutation (N=18 carriers), carriers maintained visual acuity but commonly had abnormal visual field testing, abnormal electroretinography, and mild to moderate retinal pigmentary degeneration.[9] In addition, the variability in disease severity in carriers of XLRP has complicated the ability to definitively identify the carrier state.[14-21] By analyzing patient data from 242 carriers collected over the past

four decades, the present study aims to expand our knowledge of the frequency and severity of visual function loss in XLRP carriers.

Mutations in *RP2* and in *RPGR* are primarily responsible for XLRP. In previous studies, XLRP males with *RP2* mutations tended to have lower visual acuities than those with *RPGR* mutations.[7,22] Among males with *RPGR* mutations, those with mutations in ORF15 (exon 15) tended to have a larger visual field and 30 Hz ERG amplitude than those with other mutations.[7,22,23] The 30 Hz ERG amplitude was also correlated with the position of the mutation in ORF15 (*i.e.* codon number) in males.[17] We tested whether these genotype/phenotype correlations would be apparent also in the female carriers.

Methods

Ascertainment of Patients

This retrospective study was conducted in accordance with IRB approval, HIPAA compliance, and the tenets of the Declaration of Helsinki. Patients were seen in the Electroretinography (ERG) Service of the Massachusetts Eye & Ear Infirmary by one of us (ELB) between 1970 and 2011. Two-hundred and forty-two were diagnosed as female carriers of X-linked RP based on clinical criteria, which generally required 2 affected males in the family in the absence of comparably affected female relatives and no evidence of male-to-male transmission. Molecular genetic studies of leukocyte DNA were performed in some families after 1990. The concurrent presence of high myopia was used as a risk factor for XLRP in equivocal cases.[16] Many of these carriers were relatives of males with XLRP seen in the ERG Service. Obligate carriers (n=103, with 55 in genotyped families) were narrowly defined as

having affected fathers, affected sons, or both. This narrow definition of obligate carriers was used to avoid bias in the interpretation of pedigrees in the oldest records.

Clinical Evaluation

The following measures of ocular function were analyzed when available in this review of records: best-corrected Snellen visual acuities, Goldmann perimeter kinetic visual field areas (size V-4e white test light), Goldmann-Weekers final dark adaptation thresholds to an 11 degree white test light after 30-45 minutes of dark adaptation, and full-field ERGs to 0.5 Hz and 30 Hz white flashes to monitor remaining cone + rod function and cone-isolated function, respectively. Narrow analog or digital band-pass filtering with signal averaging was used to quantify low level ERGs to 30 Hz flashes[24].

We also graded fundus appearance, using criteria similar to those of Grover *et al*[6]: Normal (grade 0); tapetal-like retinal reflex without any peripheral pigmentary retinal changes (grade 1); regional peripheral pigmentary changes involving a quadrant or hemisphere; macular RPE changes, or mild bone-spicule-like peripheral pigment (grade 2); and 3 or more quadrants of bone-spicule-like pigment or extensive peripheral areas of atrophy (grade 3).

Statistical Analysis

Data analysis was performed with JMP, version 10.0 or SAS, version 9.3 (SAS Institute, Cary, NC). Visual acuities were converted to decimals, and ERG amplitudes were transformed to natural logarithms. Since there can be discordance between eyes in XLRP carriers[1,10,25,26], each eye was considered individually except as noted otherwise.

We also calculated the percentages of carriers meeting strict and lenient clinical criteria for normality. This was based on baseline data from the initial visit (and any visits within 3

months of the initial visit). The cutoffs were 20/25 (strict) and 20/40 (lenient) for visual acuity, 0 $\log_{10}$-unit (strict) and 0.5 $\log_{10}$-unit (lenient) for final dark adaptation threshold elevation, and 11,310 deg^2 (120 deg. diameter, strict) and 10,000 deg^2 (lenient) for visual field area. These criteria were intended to have clinical relevance toward the question of whether there is a definite (strict) or possible (lenient) abnormality of these parameters. For ERG amplitudes, the cutoff values represented the lower limit of normal (strict) and half of the lower limit of normal (lenient). The normal ranges for the 0.5 Hz and 30 Hz ERG amplitudes were 350-750 μV and 50-125 μV, respectively.

For determining longitudinal exponential decay rates, repeated measures regression was performed with the MIXED procedure of SAS with code used previously for XLRP males[27] in order to make valid comparisons. Briefly, results from fellow eyes were averaged. Data were censored to remove ceiling and floor effects, and analyses were restricted to carriers with at least 3 years of follow-up (after censoring, n=37 for visual acuity, n=19 for visual field area, n=35 for 30 Hz ERG).

Half of the carriers had a mutation in either *RPGR* or *RP2*, imputed from findings in an affected male relative. To detect significant cross-sectional differences between these genotypes, an ANOVA was used that adjusted for age for all outcomes and for spherical equivalent refractive error for ERG amplitudes. Decimal visual acuity and log final dark adaptation values showed highly non-normal distributions due to ceiling effects, and thus the p values provided are from a test using normalized ranks (van der Warden test, JMP 10.0) unless otherwise stated. Age was not significantly different between genotypes (*RP2* mean 37±3 years, *RPGR* 38±1 years, unknown genotype 38±1 years, p=0.90).

Results

Patient cohort

A total of 242 female carriers from 138 families were included in the analysis. Of the 138 families, 45 tested positive for an *RPGR* mutation, 6 tested positive for an *RP2* mutation, 10 were screened but no X-linked RP mutation was detected, and 77 were not screened. In the 87 families who were not screened or who did not have an X-linked RP mutation, the diagnosis of XLRP was made based on clinical criteria (see Methods). Mutations in the female carriers were imputed from those detected in male relatives in all cases.

Similar counts can be tabulated by individual instead of by family: Of the 242 females in the study, 101 were from a family with an *RPGR* mutation; 46 of these females were obligate carriers by pedigree analysis and 55 were not. 20 females were from a family with an *RP2* mutation; 9 of these females were obligate carriers based on pedigree analysis and 11 were not. 121 females were from a family with a clinical diagnosis of XLRP (not screened for XLRP mutations or no mutation found); 48 of these females were obligate carriers by pedigree analysis while 73 were not. Females who were not obligate carriers by pedigree analysis were all affected relatives of males with XLRP.

Ages ranged from 8 months to 90 years with a median of 38 years. The number of visits per patient ranged from 1 to 8. The ethnic distribution was 91% Caucasian (including 3% Ashkenazi Jewish), 5% Asian, 2% African-American, and 2% other. There were 59 carriers followed longitudinally for at least three years, with a median follow-up of 13.5 years (range 3.5-37).

Despite the increasing accessibility and reliability of DNA sequencing over the course of the observation period, there was no “epoch” bias in the fraction of individuals with an eventual molecular diagnosis based on their initial visit date. During each decade before 2010, the

molecular diagnosis rate ranged from a minimum of 44% in carriers from the 2000s to a maximum of 54% in carriers from the 1970s.

To address the possibility of recall or selection bias, where patients may not have been motivated to return to clinic for additional visits unless symptomatic, we performed a sensitivity analysis comparing patients whose follow-up spanned > 3 years versus < 3 years; there was no statistical difference in baseline $\log_e$ ERG amplitude to 30 Hz flashes adjusted for age and spherical equivalent (p=0.43) or $\log_e$ baseline visual field area adjusted for age (p=0.72). There was, however, a small difference in baseline decimal visual acuity adjusted for age (<3 years 20/26, >3 years 20/29, p=0.003). Overall, we therefore considered that there was little evidence for extensive selection bias in the longitudinal cohort.

Cross-sectional abnormalities in retinal function

As XLRP carriers can show discordance between their two eyes[1,25,26], we initially analyzed the data with each eye considered separately. Table 1 shows that in carriers from genotyped families, the mean visual acuity of each eye was 20/27 (0.73 decimal acuity). However, the bottom fifth percentile was 20/200 (0.1). Similarly the means for visual field area, final dark adaptation threshold elevation, 0.5 Hz (cone + rod) ERG amplitude, and 30 Hz (cone-isolated) ERG amplitude all reflected considerable retinal function, while the fifth percentiles were very abnormal (Table 1).

Table 2 shows the percentage of carriers who had abnormal findings for 5 quantitative tests, considering both eyes and using lenient cutoffs to address whether the carriers suffered a clinically-relevant loss of visual function. Carriers rarely had abnormal baseline final dark

adaptation thresholds or visual acuities. It was somewhat more common, however, for carriers to have abnormal visual field areas, 30 Hz amplitudes, and 0.5 Hz amplitudes (Table 2).

As shown in Figure 1, visual acuities by eye (top) in XLRP carriers were usually normal or nearly normal. However, decreased acuity was seen even at a young age (e.g. 9 years old). Visual fields (middle) were relatively preserved. Final dark adaptation thresholds by eye (bottom) were usually normal. Figure 2 shows similar results for 0.5 Hz and 30 Hz amplitudes, except that the typical amplitudes clustered around half of the lower limit of normal. After age 30, the number of eyes with severely abnormal amplitudes appeared greater than before age 30.

Each measure of visual function was significantly related to the grade of fundus appearance ($p<0.01$). Figure 3 illustrates that mean visual acuity (top) and mean ERG amplitude to 30 Hz flashes (bottom) were highest (and comparable) for grades 0 (normal) and 1 (tapetal-like reflex) and lowest for grade 3. Nonetheless, there were carriers with reduced acuity and reduced 30 Hz ERG amplitudes who had a normal fundus or only a tapetal–like reflex. Of the carriers who were legally blind, all presented with grade 3 fundi.

There were no significant differences between *RP2* carriers and *RPGR* carriers with respect to outcome variables, including mean final dark adaptation threshold elevation (0.03 versus 0.26 log unit, $p=0.06$, age-adjusted) and mean ERG amplitude to 30 Hz flashes (geometric means 38 versus 31 µV, $p=0.20$, age- and spherical equivalent-adjusted).

The carriers with mutations in *RPGR* ORF15 (n=118 eyes) showed worse measures of visual function than those with mutations in exons 1-14 (n=84 eyes). The 30 Hz ERG amplitude (geometric mean) was 19±1.1 µV in eyes with ORF15 mutations and 32±1.1 µV in eyes with mutations in exons 1-14 ($p=0.007$ for $\log_e$ amplitude, age- and sphere- adjusted, ERG data available for n=92 eyes ORF15, n=45 eyes exons 1-14). This difference between ORF15 and

exons 1-14 eyes persisted (p=0.007) even when carriers age>65 years were excluded. The difference also persisted when the *RPGR* missense mutations (i.e. potentially less severe mutations) were removed from the dataset, leaving only nonsense and frameshift mutations (i.e. potentially null/stronger mutations). A separate comparison of missense vs. nonsense/frameshift mutations showed no significant effect on the outcome variables including $\log_e$ 30 Hz ERG (p=0.77). Lower response amplitudes in ORF15 eyes versus mutations in exons 1-14 eyes were also seen in the 0.5 Hz ERG (148±1.1 vs. 217±1.1 µV, p=0.01), and final dark adaptation threshold elevations were slightly worse in ORF15 eyes versus exons 1-14 (0.37±0.06 vs. 0.05±0.08 log unit, p=0.001). In fact, the mean final dark adaptation threshold in the exon 1-14 group (0.05±0.08 log unit) was not statistically distinguishable from normal (p>0.05). A correlation between mutated amino acid position within ORF15 and 30 Hz ERG amplitude, reported for *RPGR* males[22], was not detected (p=0.84, age-adjusted) in these female carriers, similar to findings by Pelletier *et al*[13].

Longitudinal changes

Overall, the 30 Hz cone ERGs fell, on average, by 3.7% of remaining amplitude per year (n=35 carriers, p<0.0001). Use of such exponential decay rates to estimate future progression in individual patients has been described.[28] The 30 Hz ERG amplitudes fell faster in carriers who presented with grade 2 or grade 3 fundi compared to grade 0 (normal fundus) carriers (p=0.001 and p=0.03 respectively). On average, carriers lost 0.9% (grade 0), 1.9% (grade 1), 4.1% (grade 2), and 3.2% (grade 3) of remaining amplitude per year, respectively. (A subset analysis that split the limited number of carriers into genotyped and nongenotyped cohorts resulted in a statistical model with fewer carriers that did not converge.) On average, visual field area to a V-4e white

test light did not decay significantly over time (p=0.62) for the 19 carriers evaluated longitudinally in this series.

Changes in acuity and incidence of legal blindness by fundus grade

Regression analysis showed that, on average, fundus grade 0 and 1 carriers had stable visual acuity (p=0.8 and p=0.8 respectively), while grade 2 and 3 carriers had slowly progressive visual acuity loss (p=0.04 and 0.0001 respectively). On average, $\log_e$ visual acuity changed by 0.1% (grade 0), -0.1% (grade 1), 1.4% (grade 2), and 2.3% (grade 3) per year, respectively.

However, there were exceptions to this average trend of preserved visual acuity in carriers with grade 0 or 1 fundi. Of the carriers with initially normal fundi (grade 0) or a tapetal reflex only (grade 1), there were occasional instances of progression of fundus changes and visual acuity loss. For example, one carrier with normal acuity and a grade 0, blonde fundus at age 12 later developed retinal pigment epithelial (RPE) changes, bone spicules, and atrophy, resulting in a visual acuity of 20/60 in each eye by age 43. Another carrier with a tapetal-like reflex and normal acuity at age 13 later developed depigmentation and bone spicules nasally, with vision of 20/50 OD and 20/100 OS by age 42.

Overall, including all fundus grades and all visits, five of 242 carriers (2.1%) were legally blind by visual acuity criteria (≤20/200 OU). Three of 121 (2.5%) carriers from genotyped families were legally blind, including one *RP2* and two *RPGR* families. All of the legally blind carriers had a 0.5 Hz (cone+rod) response of less than 200 µV, and all presented with a grade 2 or 3 fundi. One of these carriers initially presented only with relatively subtle depigmentation of the midperiphery. No carriers were legally blind due to visual field criteria (<20 degree diameter

OU to a V-4e white test light). In this case series, no carriers with completely normal fundi or >200 µV 0.5 Hz ERGs were legally blind. This included 43 carriers followed for more than 10 years, and 14 carriers followed for more than 20 years. However, only 8/59 carriers were followed past age 60; it is possible that some carriers will progress to legal blindness over the long term.

Of 59 carriers followed for at least 3 years, only one (~2%) became legally blind. This carrier was evaluated at age 18 with 20/30 vision OU, questionable pigment in one quadrant of one eye, a 0.5 Hz response of 152 µV OU, and a 30 Hz flicker of 41 µV OU. She was seen again at age 35 with central scotomas, 20/200 vision OU, 0.5 Hz responses of 35 µV, and a 30 Hz flicker of 12 µV. A mutation in *RP2* was detected in her affected male first cousin. Among the 242 carriers, none were legally blind due to decreased visual field (<20 degree diameter).

Rate of Carrier Detection

An analysis was carried out on the baseline data of obligate carriers in genotyped families (n=55) with standard (strict) criteria for normality. An abnormal baseline fundus exam (grade >0 in either eye) was present in only 35% of carriers. Psychophysical tests alone identified only 71% of the carriers. In contrast, ERG testing alone identified 96% (53/55). The three psychophysical tests plus ERG testing identified at least one abnormality in 100% of the carriers.

Discussion

This case series confirms that the term “carrier” can be misleading when applied to X-linked retinitis pigmentosa; many “carriers” (or more accurately, “X-linked heterozygotes”)

manifested some degree of abnormality in at least one eye. (For brevity, this study refers to both affected and unaffected X-linked heterozygotes as "carriers".) Nearly half of the carriers had abnormal psychophysical testing, and 2% of carriers were legally blind. A previous study describing a large kindred with a frameshift *RPGR* mutation showed preservation of visual acuity of at least 20/50[9], perhaps due to the smaller sample size or to the characteristics of the mutation itself.

A previously published case series[6] found that carriers who presented with grade 0 or grade 1 fundi did not progress to higher grades or visual loss. Our data showed that 7% (7 of 106) who presented with grade 0 and grade 1 fundi had decreased visual acuity (<20/40 in both eyes, at any visit). Two of those carriers presented with normal acuity and progressed, while the other 5 initially presented with decreased acuity. However, no baseline grade 0-1 carriers were observed to be legally blind. More detailed criteria to predict future maculopathy and related visual acuity changes in carriers are yet to be defined. Modifier loci have been detected in males with *RPGR* mutations[23]; such loci may also have effects in female carriers.

In the rare instances where carriers became legally blind, it was due to decreased visual acuity and not from visual field loss. This was similar to our previously published observation that legal blindness in males with XLRP due to *RPGR* mutations was also typically due to loss of visual acuity and not visual field.[27] In fact, the observed loss of visual acuity and 30 Hz ERG (cone) amplitude compared to the relatively preserved visual field area and 0.5 Hz ERG (cone-plus-rod) amplitude suggest that the XLRP carrier state is a cone-predominant phenotype; a similar pattern has been previously reported in XLRP males, especially in males with mutations near the 3' end of *RPGR* ORF15.[22,29]

Female carriers with mutations in *RPGR* ORF15 showed worse measures of visual function than carriers with mutations in exons 1-14. This is in agreement with one study that found worse function in ORF15 families[10], but is in contrast to other studies[7,22,23,29] in males with *RPGR* mutations which showed an effect in the opposite direction. The reason for this is not known.

With regard to identification of carriers based on clinical testing, the 96% (53/55) detection rate by ERG in this report among obligate carriers was the same as our laboratory's prior results based on only 23 carriers.[15] Therefore, normal ERGs in both eyes, in at-risk female family members, suggest that the carrier state of XLRP is unlikely.

When a fundus abnormality is present in a female with more severely affected male relatives, it may not be straightforward to make a definite diagnosis of the carrier state of XLRP based on clinical data alone. It is important to see the phenotype in the affected male relatives to confirm that they have RP (and not, for example, choroideremia). Furthermore, the female could have sector RP, dominant RP with incomplete penetrance, or pericentral RP — all of which can present with mild RP phenotypes.[30-32]

There still remains a place for other modalities of carrier detection. Increasingly, molecular genetic testing is being used and is becoming less expensive, though the tests should be performed in a laboratory familiar with the challenges of *RPGR* gene sequencing, and confirmatory testing in family members, particularly males, may be helpful.[7,33] Recent advances in imaging have shown that reflectance and OCT abnormalities are present in XLRP carriers with tapetal-like reflexes.[21] However, the sensitivity and specificity of these imaging tests in carriers with ophthalmoscopically-normal fundi are not known. That being said, seeing a tapetal-like reflex and/or characteristic signs on imaging may be useful in positively identifying a

carrier. However, even detection of a tapetal-like reflex may not be diagnostic of the carrier state of XLRP.[34]

The above observations raise the question as to how this variability in phenotype is produced. In the Lyon hypothesis of random X-chromosome inactivation during embryogenesis, as originally described[35], an organism can be more or less affected depending on the proportion of tissues that happened to descend from cells that inactivated either the mutant or wildtype X chromosome.[26] The resulting patterns of random X inactivation have been explicitly demonstrated in the retinas of mice[26], which show mosaic patterns within the retina, random variation in the total amount of retina affected, as well as interocular differences in severity. Mosaic patterns can also be seen in some human XLRP carriers evaluated *in vivo* with advanced imaging techniques[21], and in one case, histology of eyes from a human carrier eye showed "patchy" degeneration[36]. In the present study, the observations that the ERG responses were, on average, approximately half the lower limit of normal (dotted lines, Figure 2), and that the mean 30 Hz amplitude rate of decay was half of that of fully affected XLRP males (3.7% vs 7.4%) are remarkably consistent with the Lyon hypothesis of random X-chromosome inactivation. Like the patterns of X-inactivation seen in mouse retinas[26], in human carriers of XLRP half of the retina appears to be affected, on average, but with a wide distribution of severity.

In conclusion, while many XLRP carriers have mild or moderate abnormalities and 2% become legally blind due to loss of acuity, visual field area was relatively preserved and no carriers went completely blind (no light perception). XLRP males, with a median age of legal blindness of 45 years[27], were on average much more affected than the female carriers reported in this case series. From a family-planning perspective, it is important to counsel carriers that

affected males have a worse visual prognosis than female carriers, and that, while rare, even female carriers can have significant impairment of retinal function.

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Figure Legends

Figure 1. Vision as a function of age among carriers of X-linked RP. Visual acuity (A), visual field equivalent circular diameter (B), and final dark adaptation threshold elevation (C) are plotted for every visit in the database, with each eye plotted individually. Data points have been shifted slightly to facilitate visualization of overlapping points.

Figure 2. Distribution of ERG findings by age among carriers of X-linked RP. The 0.5 Hz (cone+rod, panel A) amplitudes, and the 30 Hz (cone, panel B) amplitudes are plotted for every visit, with each eye plotted individually. The solid horizontal lines represent the lower limits of normal for 0.5 Hz amplitudes (50 □V) and 30 Hz amplitudes (350 □V). The dashed horizontal lines represent half of the lower limits of normal, and the plotted values tend to cluster around these values. Panel C shows the average 30 Hz flicker amplitude only for carriers with more than one datapoint to better visualize the rate of decay of the ERG responses.

Figure 3. Increasingly severe abnormalities seen on fundus exam are correlated with lower visual acuity (top, $p<0.0001$) and 30 Hz ERG amplitudes (bottom, $p<0.0001$, age- and sphere-adjusted). The genotyped subset of carriers (*RPGR* or *RP2*) is shown. See text for grading schema. Briefly, Grade 0: normal. Grade 1: tapetal-like reflex only. Grade 2: regional pigmentary changes. Grade 3: diffuse pigmentary changes. Diamonds show means and 95% confidence intervals of the mean.

Table 1

Test	Mean +/- S.D. (N)	Mean (clinical units)	Lower limit of normal	Bottom 5%
Visual acuity	0.73 ± 0.27 (242) decimal	20/27	20/20	20/200
Visual field equivalent diameter	9.20 ± 0.85 (108) $\log_e$ (deg^2)	113 deg.	120 deg.	86 deg.
30 Hz ERG amplitude	3.31 ± 0.96 (129) $\log_e$ µV	28 µV	50 µV	7 µV
0.5 Hz ERG amplitude	5.29 ± 0.79 (124) $\log_e$ µV	200 µV	350 µV	56 µV
Dark adaptation final threshold elevation	0.14 ± 0.43 (158) log units	0.14 log units	0 log units	1 log unit

Table 1. Average baseline findings for all carriers in genotyped families, by eye. N represents the number of eyes. The visual field equivalent diameter is calculated as if the recorded visual field area were a circle. Not all tests were performed on every patient at the first visit.

Table 2

Outcome	Percentage of carrriers (number of carriers) All	In genotyped families
Dark adaptation abnormal (>0.5 logs)	10% (21/215)	9% (10/110)
Visual acuity abnormal (<20/40)	20% (48/241)	21% (25/121)
30 Hz ERG abnormal (<25 μV)	35% (49/139)	32% (21/65)
Visual field abnormal (<10,000 deg. sq.)	37% (38/103)	31% (17/54)
0.5 Hz ERG abnormal (<175 μV)	41% (54/132)	39% (25/64)
At least one psychophysical test (VA, VF, DA) abnormal	49% (43/87)	40% (20/50)
Visual acuity <20/40 in both eyes at any visit	11% (27/242)	9% (11/121)
Visual acuity ≤20/200 in both eyes at any visit	2.5% (6/242)	2.5% (3/121)

Table 2. Percentages of carriers that were abnormal in one or both eyes. For patients with multiple visits, values are from the baseline visit. Not all tests were performed on every patient at the first visit.

Table 3

Outcome	Percentage of carrriers (number of carriers) All	In genotyped families
30 Hz ERG amplitude abnormal (<50 µV)	89% (50/56)	83% (24/29)
0.5 Hz ERG amplitude abnormal (<350 µV)	84% (46/55)	75% (21/28)
Visual acuity abnormal (<20/25)	55% (57/104)	47% (26/55)
Visual field abnormal (120 deg. equiv. diameter)	59% (22/37)	59% (13/22)
Dark adaptation abnormal (>0 log units)	17% (16/96)	20% (10/51)
At least one psychophysical tests (VA, VF, DA) abnormal	71% (25/35)	71% (15/21)
ERG 0.5 Hz amp. or 30 Hz amp./timing abnormal	96% (53/55)	93% (26/28)
Any test (VA, VF, DA, 0.5 Hz amp., 30 Hz amp.) abnormal	100% (28/28)	100% (15/15)

Table 3. Carrier detection in obligate carriers from baseline visit data. Percentages represent the fraction of obligate carriers abnormal in either eye, with cutoff values strictly defined as to detect as many carriers as possible.

Figure 1

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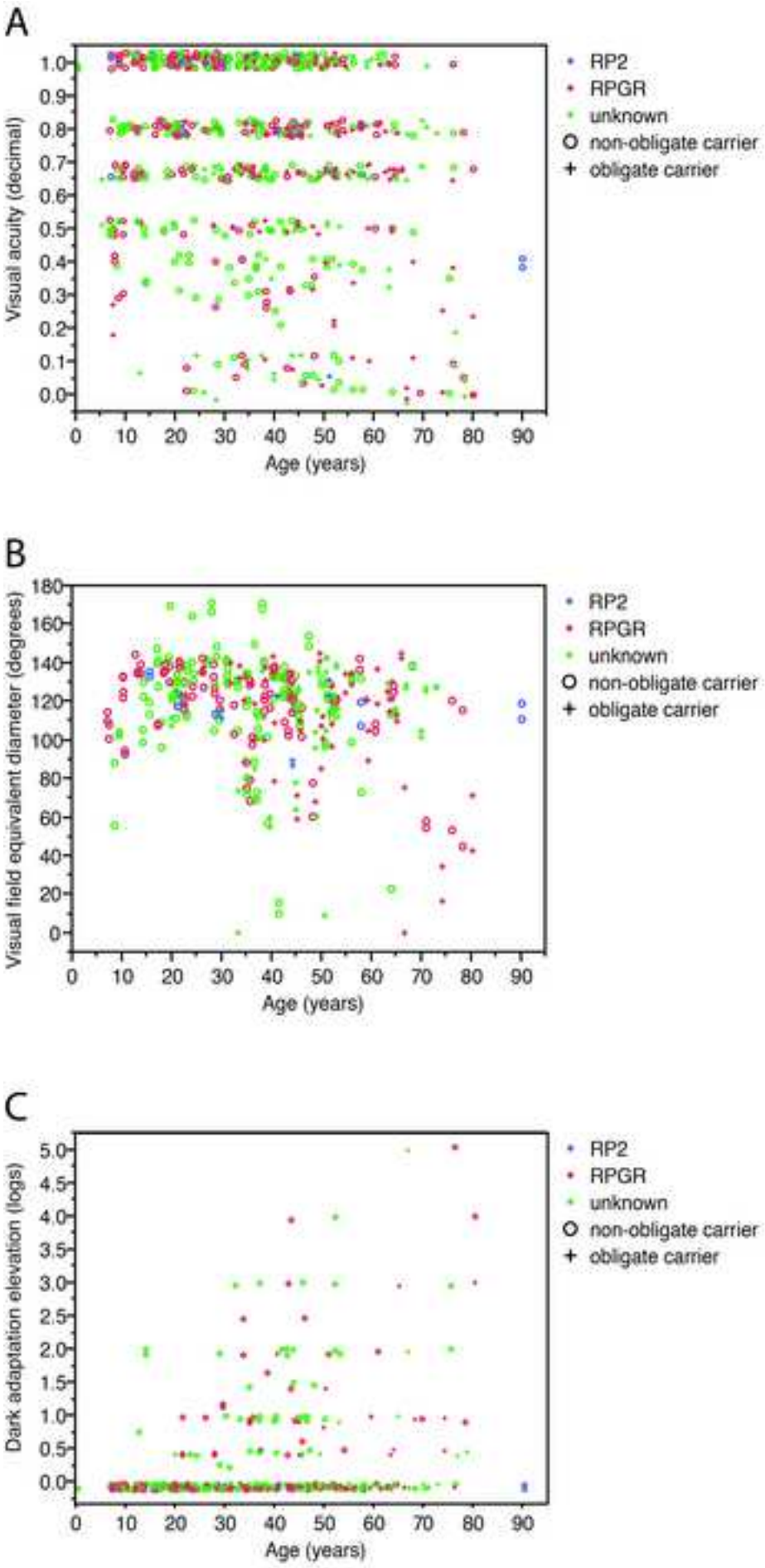

Figure 2

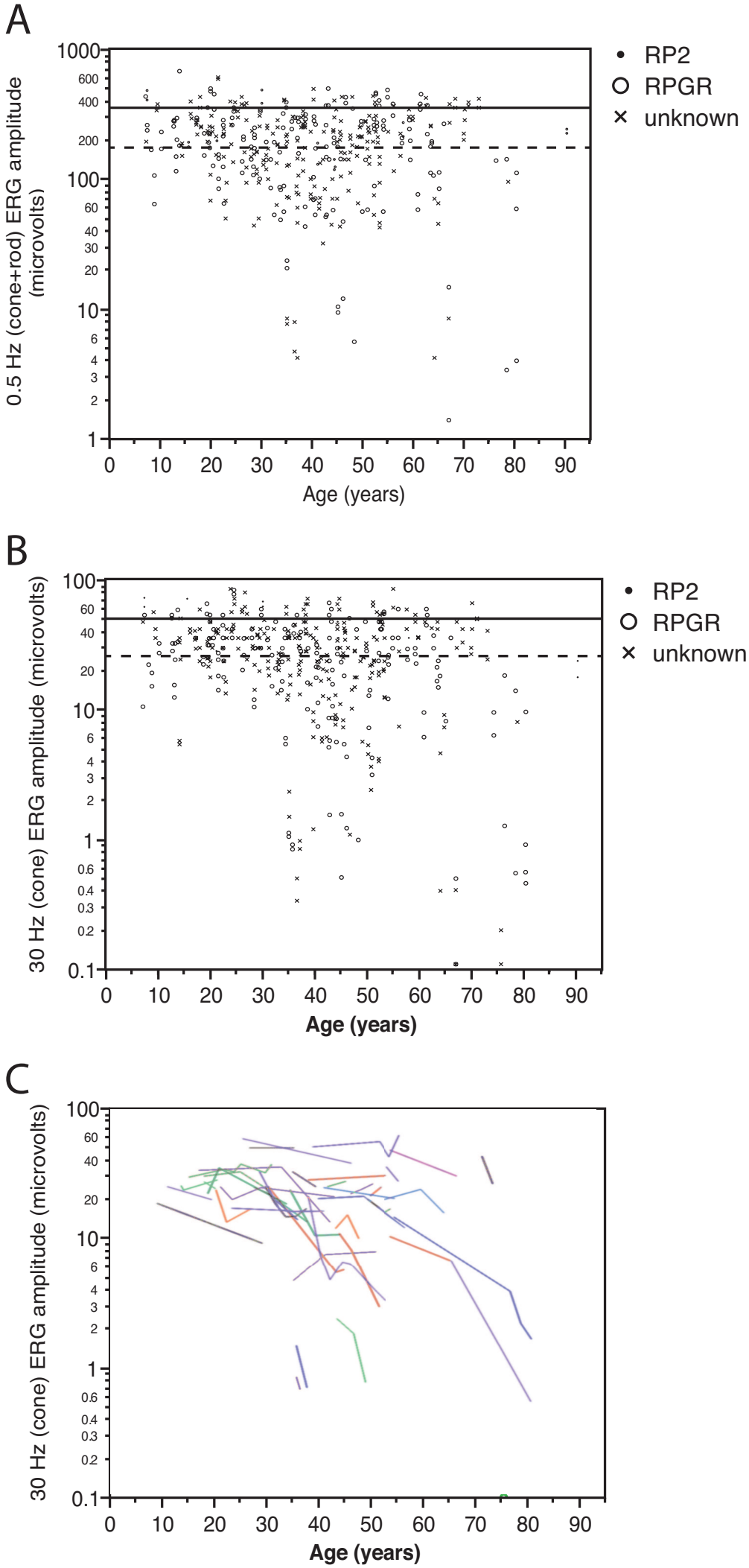
A
0.5 Hz (cone+rod) ERG amplitude (microvolts)
Age (years)
RP2
RPGR
unknown
B
30 Hz (cone) ERG amplitude (microvolts)
Age (years)
RP2
RPGR
unknown
C
30 Hz (cone) ERG amplitude (microvolts)
Age (years)

Figure 3
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