X-Linked Recessive Atrophic Macular Degeneration from *RPGR* Mutation

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We mapped a new X-linked recessive atrophic macular degeneration locus to Xp21.1–p11.4 and show allelic involvement of the gene *RPGR*, which normally causes severe peripheral retinal degeneration leading to global blindness. Ten affected males whom we examined had primarily macular atrophy causing progressive loss of visual acuity with minimal peripheral visual impairment. One additional male showed extensive macular degeneration plus peripheral loss of retinal pigment epithelium and choriocapillaries. Full-field electroretinograms (ERGs) showed normal cone and rod responses in some affected males despite advanced macular degeneration, emphasizing the dissociation of atrophic macular degeneration from generalized cone degenerations, including X-linked cone dystrophy (COD1). The *RPGR* gene nonsense mutation G→T at open reading frame (ORF)15+1164 cosegregated with the disease and may create a donor splice site. Identification of an *RPGR* mutation in atrophic macular degeneration expands the phenotypic range associated with this gene and provides a new tool for the dissection of the relationship between clinically different retinal pathologies.

Key Words: macular degeneration, *RPGR*, nonsense mutation, atrophic, splice site, RP3, CSNB1, *NYX*, X-linked

INTRODUCTION

Macular degeneration is a leading cause of visual impairment in the United States. Several mendelian forms of macular degeneration have been mapped and some genes have been cloned, but none thus far on the X chromosome, except for deletions in red and green color genes at Xq28 associated with progressive cone dystrophy and unusual cases with progressive macular atrophy in families with blue cone monochromacy [1–3]. The X chromosome harbors several retinal disease loci, including that for cone dystrophy (COD1 and COD2), juvenile retinoschisis (XLRS), congenital stationary night blindness (CSNB), and at least five loci for retinitis pigmentosa (RP; http://www.sph.uth.tmc.edu/Retnet/), with considerable overlap of genetic intervals for some of the retinal disease phenotypes mapping to Xp [4]. Cloning the genes responsible for X-linked recessive traits of XLRS, retinitis pigmentosa 2 (RP2), retinitis pigmentosa 3 (RP3), and congenital stationary night-blindness (CSNB1) has allowed exploration of whether these diseases are allelic to other retinal dystrophies that localize to overlapping genetic intervals.

We studied a large five-generation pedigree, UM:F1088, in which atrophic macular degeneration segregated as an X-linked recessive trait [5]. Among 11 affected males whom we examined, 10 showed predominant atrophic macular degeneration with negligible or modest peripheral retinal involvement. Only one affected male had peripheral degeneration that mimicked retinitis pigmentosa (RP). Linkage and haplotype analysis mapped the trait to a 15-cM interval at Xp21.1–p11.4 that excluded many of the known X-chromosomal retinal disease loci. The remaining critical interval encompassed the nyctalopin (*NYX*) gene associated with CSNB1 and the retinitis pigmentosa GTPase regulator (*RPGR*) gene causing RP3. Mutation analysis of the *RPGR* gene identified a nonsense mutation that segregated completely with the disease in family UM:F1088.

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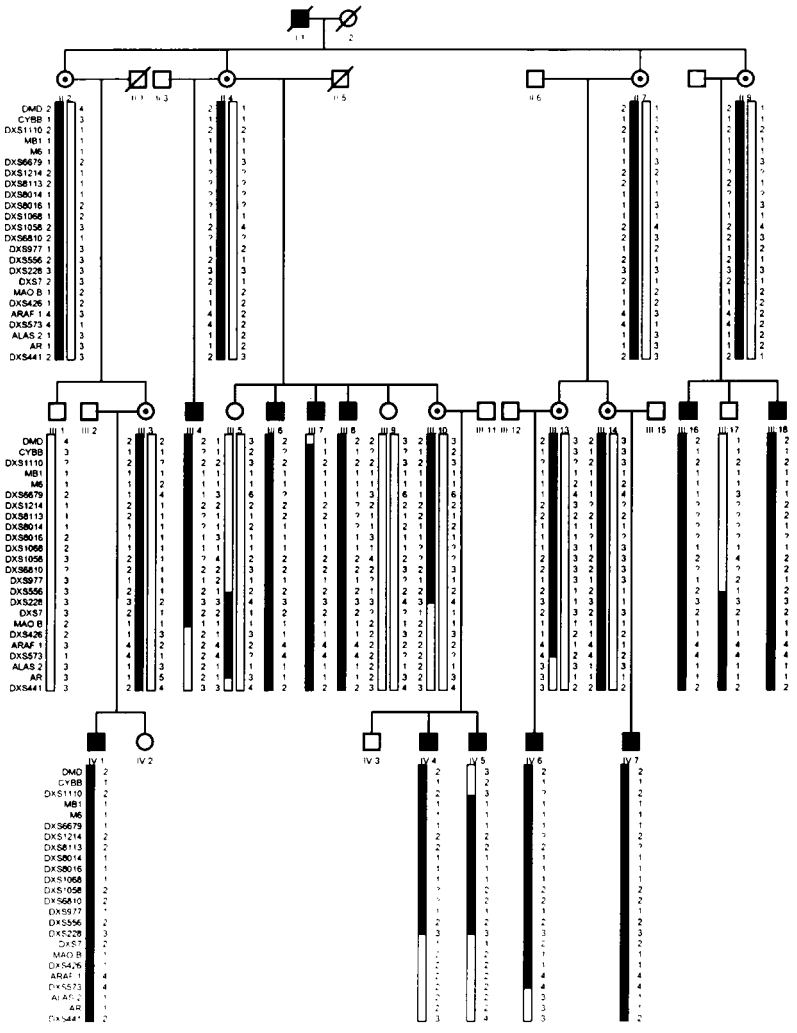

FIG. 1. Pedigree of family UM:F1088 and haplotypes with selected informative markers on the X chromosome. Filled squares signify affected males; open squares indicate unaffected males. Dotted circles are female obligate carriers. Filled regions of bars indicate the disease haplotype. Question marks in the haplotype denote PCR amplification failure. Pedigree was edited by excluding results on additional branches of the pedigree that do not alter the conclusions.

RESULTS

Clinical Characteristics

Among the 11 affected males in family UM:F1088 (Fig. 1), 10 had macular degeneration that caused progressive visual acuity loss as the presenting symptom. The 48-year-old proband III-16 had acuities of 20/50 and 20/200 when we first examined him. He reported a 5-year history of progressive central vision loss, but had good acuity when younger and had completed military service during his 20s without difficulty. At age 48 the fundus of both eyes showed a circumscribed central macular area of atrophy of the retinal pigment epithelium (RPE; Fig. 2). The midperipheral retina showed hypopigmentation from RPE thinning but without intraretinal pigment clumping or loss of choriocapillaris by fluorescein angiography (FA). These RPE changes were disproportionate to his 5 diopters of myopia. Caliber of the retinal vessels was essentially normal. Visual-field extent was normal to both large and small targets except for a central scotoma (Fig. 3). Full-field ERG responses had normal waveform, amplitude, and implicit times for both dark- and light-adapted states and 30-Hz flicker (Fig. 3). Within 1 year, his acuities dropped to 20/200 in both eyes and then to 20/400 2 years later. However, repeated ERGs continued to show normal rod and cone responses (Fig. 3), indicating that the majority of changes were localized to the macula rather than involving the entire retina in widespread fashion.

Macular degeneration was also the principal finding in his brother and nine male cousins of first and second degree, ranging in age from 27 to 71 years old, and all had acuities of 20/200 or worse except IV-5 (Fig. 2). Individual IV-5 retained 20/25 acuity at age 31, but a fluorescein angiogram showed a hyperfluorescent ring of parafoveal loss of RPE integrity, and his acuity subsequently dropped to 20/200 within a few years. His brother, IV-4, had quite extensive atrophic macular degeneration by age 27 (Fig. 2) that resulted in extensive central visual field loss and some ERG reductions of both cone and rod function (Fig. 3). Neither IV-4 nor IV-5 was myopic, but the remaining affected males ranged from –3 to –13 diopters of myopia. None of these individuals reported problems with visual sensitivity at night, except male IV-6 who had extensive peripheral retinal degeneration. Dark-adaptation thresholds remained normal or were < 1 log unit elevated in these affected men, except for male IV-6. The oldest tested by ERG was age 59 and had slightly reduced rod and cone amplitudes that were partially due to his high myopia of –8 diopters (III-4 in Fig. 2). He reported marked acuity loss over a 3-year period in his 50s, and his acuity was 20/300 for both eyes by age 59.

We examined 12 obligate carrier females, and all exhibited subtle perimacular RPE depigmentation, with golden-yellow discoloration in thin radial lines that gave a "tepetal reflex." Most of them also had peripheral regions of RPE depigmentation, as did many of the affected males. The carriers did not have acuity loss, and their color discrimination

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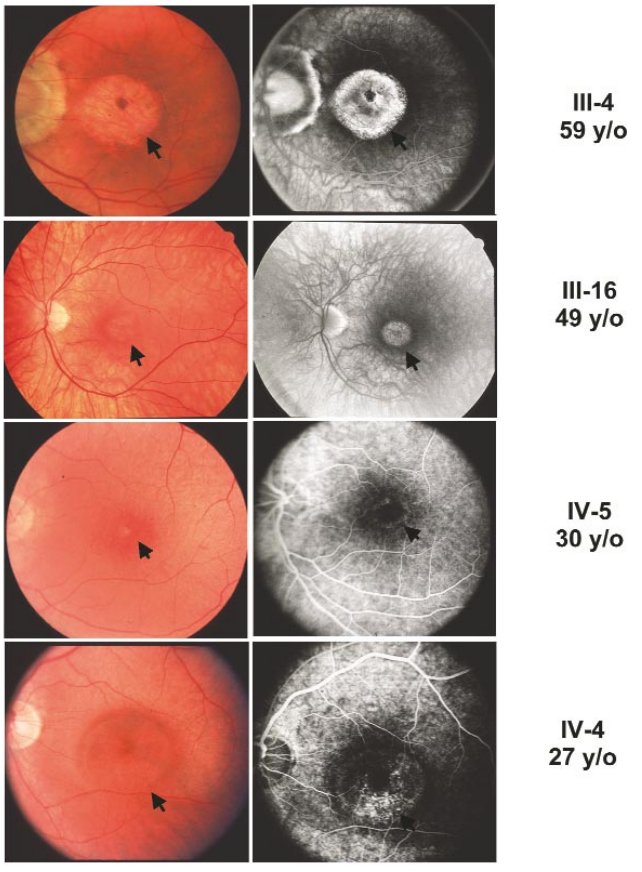

FIG. 2. Color fundus photographs and black-and-white fluorescein angiograms (FA) of four affected males from family UM:F1088. Clinical changes were essentially identical for both eyes of all cases. Left eyes are shown here. III-16, proband, at age 51 years old (y/o), had bilateral 20/200 acuities from a circular zone of atrophic loss of the retinal pigment epithelium (RPE) extending 1 disc-diameter (DD) across the center of the macula and resulting in FA hyperfluorescence; retinal vessel caliber was essentially normal; myopia caused slight RPE retraction from around the optic nerve head. III-4, 59 y/o, had bilateral 20/300 acuities from extensive macular RPE atrophy across the central 1-DD region and extensive myopic RPE retraction from around the nerve head. For IV-5, 30 y/o, FA showed a slight hyperfluorescent parafoveal ring of early RPE atrophy, but relative preservation of the central fovea still provided bilateral 20/25 acuities; there was slight myopic RPE retraction from around the nervehead. IV-4, 27 y/o, had bilateral 20/200 acuities from extensive atrophic macular degeneration across the central 1.5 DD, and slight myopic RPE retraction from around the nervehead.

was normal on D-15 testing. ERGs on six female carriers had normal rod and cone responses, even the oldest, who was 70 years of age.

No affected males or carrier females in this family developed choroidal neovascular processes associated with the "wet" or "hemorrhagic" form of macular degeneration, including the oldest examined (affected males, ages 59, 71; carrier females, ages 63, 70, 80). From the clinical picture, we characterized the predominant phenotype in this family as an X-linked atrophic macular degeneration.

Genetic Analysis

Linkage analysis initially was conducted with markers spanning the entire X chromosome. Markers at loci corresponding to RP6, RP2, RP23, RP24, COD2, XLRS, and the red–green color genes all gave lod scores of $-\infty$ at zero recombination fraction, thereby excluding these loci as causative in this family (Table 1). Marker *DXS1058*, linked to the retinitis pigmentosa 3 (RP3) locus, gave a lod score of 4.17 at zero recombination fraction, mapping the disease gene to Xp21.1–p11.4. A systematic analysis of linkage and haplotype was then carried out by genotyping with > 40 microsatellite markers at Xp21.1–p11.4. Markers *DXS6679*, *DXS8113*, *DXS8016*, *DXS6810*, *DXS977*, and *DXS556* gave significant positive lod scores at zero recombination fraction (Table 1), localizing the disease gene to the interval between markers *DXS1110* and *MAOB*. Haplotype analysis confirmed *DXS1110* and *DXS7* as the flanking markers for the 15-cM critical interval in family UM:F1088 by identifying recombination events in an obligate carrier female (III-9) and an affected male, IV-5 (Fig. 1).

The critical interval in this pedigree encompassed 36 expressed sequence tag (EST) clusters that represent potential transcripts and the genes *RPGR* and *NYX* (http://www.ncbi.nlm.nih.gov/genome/guide/human/). Because *NYX* and *RPGR* are associated with retinal diseases CSNB1 and RP3, respectively, we sequenced both genes to search for mutations. No mutations were found in any exon of *NYX*.

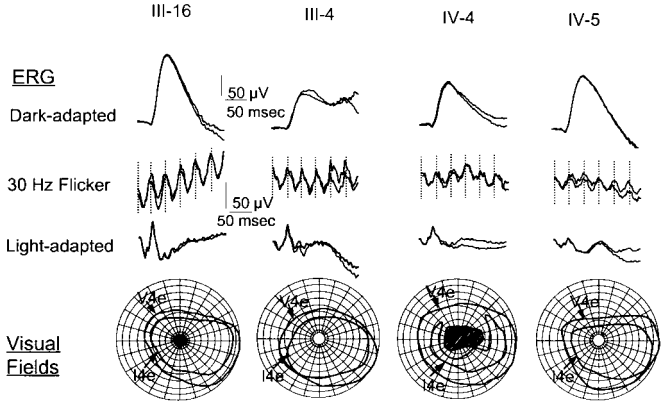

FIG. 3. ERG response and visual fields of the four affected males shown in Fig. 2 from family UM:F1088. III-16 had normal rod and cone ERG responses (dark-adapted rod b-wave of 320 μV, light-adapted photopic response of 60 μV, and 30-Hz flicker of 65 μV with normal implicit time; two responses are shown for each condition). III-4 had nearly normal rod and cone ERG single-flash responses after accounting for his –8 diopter myopia, but 30-Hz cone flicker was slightly delayed. IV-4 and IV-5 both had normal rod b-wave amplitude but modestly reduced photopic amplitude, and reduced and delayed 30-Hz flicker response. Visual fields were normal for all using large (V4e) and small (I4e) targets, except for the central losses expected from macular degeneration.

TABLE 1: Two-point lod scores of markers on X-chromosome versus UM:F1088 family

	Recombination fraction								
Marker	.01	.05	.10	.20	.30	.40	r	Z	r(-2)
KALLMAN	-0.51	0.12	0.32	0.42	0.36	0.22	.20	0.42	.00
DYS II	0.76	1.90	2.18	2.06	1.60	0.91	.13	2.20	.00
CYBB	-0.22	0.39	0.58	0.62	0.51	0.30	.17	0.63	.00
DXS 1110	-0.51	0.12	0.32	0.42	0.36	0.22	.20	0.42	.00
DXS 6679	4.75	4.46	4.08	3.27	2.34	1.27	.00	4.82	.00
DXS1214	0.79	0.70	0.60	0.40	0.25	0.12	.00	0.82	.00
DXS8113	2.66	2.47	2.21	1.67	1.08	0.45	.00	2.71	.00
DXS8014	0.60	0.56	0.52	0.41	0.29	0.16	.00	0.61	.00
DXS8016	2.49	2.33	2.13	1.68	1.19	0.64	.00	2.53	.00
DXS 1068	1.19	1.12	1.02	0.82	0.58	0.32	.00	1.20	.00
DXS 1058	4.11	3.85	3.52	2.79	1.98	1.07	.00	4.17	.00
DXS6810	2.82	2.59	2.29	1.68	1.06	0.47	.00	2.87	.00
DXS 977	4.15	3.90	3.57	2.86	2.05	1.11	.00	4.21	.00
DXS 556	4.15	3.88	3.53	2.76	1.91	0.96	.00	4.21	.00
DXS 228	1.48	1.39	1.28	1.02	0.73	0.40	.00	1.51	.00
DXS 7	0.46	1.62	1.92	1.86	1.46	0.84	.13	1.96	.00
MAOB	-0.41	0.77	1.09	1.08	0.74	0.23	.14	1.15	.00
DXS 426	-1.55	0.30	0.87	1.06	0.80	0.35	.18	1.08	.00
ARAF	-1.54	0.35	0.97	1.26	1.09	0.66	.20	1.26	.00
DXS 573	-1.24	0.60	1.18	1.39	1.15	0.68	.18	1.40	.00
ALAS 2	-3.54	-0.95	-0.03	0.58	0.64	0.42	.26	0.66	.02
AR	-3.24	-0.65	0.27	0.86	0.87	0.56	.25	0.91	.02
DXS 441	-5.24	-1.95	-0.73	0.19	0.42	0.32	.31	0.42	.04
DXS 458	-3.32	-1.33	-0.57	0.03	0.21	0.18	.33	0.22	.02
DXS 456	-2.73	-0.79	-0.10	0.34	0.35	0.17	.25	0.38	.01
DXS 454	-1.40	-0.72	-0.44	-0.19	-0.08	-0.02	.50	0.00	.00
DXS 425	-1.91	-0.61	-0.12	0.22	0.29	0.20	.29	0.29	.00
DXS 294	-4.89	-2.81	-1.92	-1.06	-0.57	-0.24	.50	0.00	.09
FRA X	-5.02	-2.33	-1.26	-0.37	-0.01	0.09	.40	0.09	.06
DXS 52	-6.42	-3.05	-1.71	-0.56	-0.09	0.07	.42	0.07	.08
FAC VII	-8.12	-4.09	-2.48	-1.08	-0.44	-0.12	.50	0.00	.12

We identified a nonsense mutation, G→T at ORF15+1164 of *RPGR*, in affected individuals of family UM:F1088 (Fig. 4). In addition, this sequence change was also predicted to create a novel donor splice site with a score of 0.83 and 0.99 using gene analysis software (http://www.fruitfly.org/seq_tools/splice.html and http://www.cbs.dtu.dk/biolinks/pserve2.html, respectively). This mutation segregates with the disease in this family in all meioses that we studied, and we did not find it in 100 unrelated control chromosomes tested. All obligate carriers in the family UM:F1088 showed the presence of this mutation in the heterozygous state. All the remaining exons of *RPGR* showed no mutations.

DISCUSSION

The important message of this study is that the phenotype of severe atrophic macular degeneration is allelic to the RP3 form of X-linked retinitis pigmentosa disease, which typically has quite early and retinal widespread involvement of rod photoreceptors resulting in debilitating night-blindness and peripheral vision loss by the teenage years and with nearly total blindness by early adult age. By contrast, the affected males in our family, UM:F1088, suffer primarily central vision loss but retain peripheral visual function even in advancing age. Identification of a nonsense mutation in *RPGR* exon ORF15 in this family demonstrates the involvement of *RPGR*

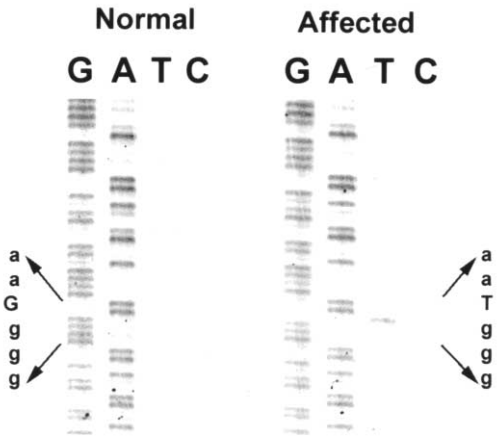

FIG. 4. Sequence showing ORF15+1164 G→T mutation in affected and unaffected individuals. The nucleotides flanking the mutation are shown.

with macular dystrophy. This adds *RPGR* to the list of retinal genes associated with pleiotropic disease phenotypes that encompass both retinal degeneration and macular degeneration, including *RDS*/peripherin and the stargardt *ABCA4* [6–8].

We examined one male with early stage disease (IV-5). He had 20/25 acuity (implying an adequate number of foveal cone photoreceptors remaining), but fluorescein angiography showed an atrophic ring developing around the fovea, indicating early-stage disease of the parafoveal RPE. A similar pattern of involvement has been reported for age-related macular degeneration in autopsy eyes [9], which show structural changes first for the parafoveal zone, containing both rods and cones, while sparing the central fovea, which has exclusively cones, thus implicating rods rather than the cones in the initial disease pathway, or possibly an interdependence of rod and cone photoreceptors, as was proposed for retinitis pigmentosa [10]. Incidentally, an initial relative sparing of the central-most foveal cones despite progressive pathology in the surrounding annular zone would explain the rapid progression of loss of acuity reported by these affected males once the degenerative process becomes clinically apparent.

The appropriate terminology to describe this phenotype could be debated, regarding whether or not it is a variation on the theme of "cone dystrophy." Macular involvement, including outright macular atrophy [11], occurs in some panretinal cone dystrophy; but cone dystrophies more typically lack outright macular atrophy and show only granularity of macular RPE pigmentation [12]. Furthermore, isolated cases [13,14] and mendelian family pedigrees [15] are reported in which foveal cones are dysfunctional despite no observable fundus abnormalities, lending support to a biological distinction between peripheral versus foveal cone pathology. Hence the extensive structural degeneration of the macula in this family is not prototypical for cone dystrophy.

Macular degeneration is rarely reported as a strong mendelian trait on the X chromosome, except in a few small pedigrees involving the red–green opsin genes at Xq28 [1–3], both reported for quite small families. Although some individuals in X-linked "cone dystrophy" families (COD1) [16] have macular degeneration, a recent report of 10 affected males in an extensive COD1 family indicated only irregular macular pigmentation, and none had "bull's-eye" macular changes [17].

The mutation in family UM:F1088 is predicted to result in premature termination of the *RPGR* protein and the loss of 180 amino acids at the C terminus. The N-terminal region of the *RPGR* protein encoded by exons 2–9 is homologous to the regulator of chromatin condensation (RCC1) [18]. The terminal exon of ORF15 of retina-specific transcript codes for a well-conserved, repetitive, glutamic acid- and glycine-rich domain. The truncated protein that is predicted for this nonsense mutation observed in family UM:F1088 would retain the RCC1 domain, but 15 out of the 27 imperfect repeats of 15–33 nucleotides at the C-terminal end would be missing. The functional importance of this repeat region is not known.

Besides losing the 15 imperfect repeats, this nonsense mutation might also create a new donor splice site and lead to an alternatively spliced variant of the *RPGR* with additional exons. Regaining any one or all of the downstream exons [16–19] of the *RPGR* as a result of a novel splice donor site would cause a frameshift. Future experiments will be needed to understand the pathobiology of the macular degeneration in this family due to the mutation in *RPGR*.

A wide range of *RPGR* mutations that result in premature termination of at various lengths is reported in families with typical symptoms of RP3-type retinitis pigmentosa [19–23]. RP3 patients have widespread rod and cone degeneration at young ages and progress to global blindness rather than having selective macular degeneration. In some cases, RP3 female carriers also show considerable retinopathy (in addition to the affected males), as described for a 1-bp insertion in the *RPGR* exon ORF15 [24], but this family did not have disproportionate macular degeneration. In a different case, a 4-bp deletion in the *RPGR* exon ORF15 was identified in a patient diagnosed as having "probable" X-linked cone dystrophy [19]. Irrespective of the involvement of cone photoreceptors, patients reported with *RPGR* mutations generally show widespread abnormal rod function and have peripheral field loss, neither of which occurred in the affected men in our family UM:F1088.

Whether *RPGR* is expressed in cones is not yet resolved. The RPGR protein has been detected in both rod and cone photoreceptors using antibodies raised against the residues 494–563, which are common to all *RPGR* variants including the predominant retinal transcript ORF15 [25]. However, antibodies raised against the N-terminal region indicate *RPGR* expression only in rods and not in cones [26]. This might indicate alternatively spliced forms. *RPGR* mutant mice showed cone function loss earlier and more severely than rod function loss [27]. Given this result, it may not be surprising that the *RPGR* is associated with cone dysfunction and possibly with a macular degeneration phenotype during some stage of

human RPGR disease. However, in family UM:F1088 the loss of macular cones occurs semiselectively and is quite disproportionate to the minimal peripheral involvement. Understanding the processes by which the macula is targeted semispecifically in this family, and mechanisms by which macular cones are lost, should provide further clues to the nature of macular degeneration.

MATERIALS AND METHODS

Clinical studies. Informed consent was obtained from all participating individuals using approved procedures. Visual fields were evaluated by Goldmann perimetry using V4e and I4e white targets. Color discrimination was tested using the Farnsworth panel D-15 under standard MacBeth lighting, and conventional scoring was used to detect discrimination errors along protan, deutan, or tritan axes [2]. Ganzfeld (full-field) ERGs were recorded as described [28]. Absolute-threshold sensitivity was measured at six positions from 20° temporal to 60° nasal retina across the horizontal meridian after 1 hour of dark adaptation, using a Goldmann–Weekers dark adaptometer with 0.8-second flashes of a 5.7° target; thresholds are reported with reference to normal mean rod final thresholds determined for 25 control subjects. For the moderate to high myopia exhibited by many of the affected males, ERG norms are subnormal [29].

Genotyping. DNA was extracted from leukocytes of 23 members of pedigree UM:F1088 (Fig. 1), including 11 affected males, 2 unaffected at-risk males, 8 obligate carrier females, and 2 females at risk of being carriers. Genotyping with microsatellite markers was done as described [28]. Description of the polymorphic markers and genetic distances were obtained from the Genome database (http://www.gdb.org/). The forward primer for each microsatellite was end-labeled with γ-[^{32}P]dATP [30]. The PCR products were separated by denaturing gel electrophoresis and visualized by autoradiography.

Linkage analysis. Two-point linkage analysis was done using the program MENDEL [31], with marker allele frequencies estimated by maximum likelihood [32]. Individuals with normal vision were considered unaffected if over the age of 50. The disease was coded as a fully penetrant X-linked recessive trait with a gene frequency of 0.0001 for the disease allele.

Mutation analysis. Primers used to sequence exons of *RPGR* are described elsewhere [18,33]. All three exons of *NYX* were sequenced using primers obtained from K. T. Hiriyanna *et al.* (pers. comm.). Exons were amplified by PCR, and sequencing was done using a ^{33}P-cycle sequencing reaction kit (Amersham, Arlington Heights, IL).

Sequence analysis. The sequence of the *RPGR* gene incorporating the sequence change observed in the pedigree UM:F1088 was analyzed (using the software at http://www.fruitfly.org/seq_tools/splice.html and http://www.cbs.dtu.dk/biolinks/pserve2.html) to detect possible novel splice sites created as a result of the alteration in the sequence.

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