Disease Course of Patients with X-linked Retinitis Pigmentosa due to *RPGR* Gene Mutations

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Purpose. To measure the rates of visual acuity, visual field, and ERG loss in patients with X-linked retinitis pigmentosa due to *RPGR* mutations and to determine whether these rates differ from those of patients with dominant retinitis pigmentosa due to *RHO* mutations.

Methods. Snellen visual acuities, Goldmann visual field areas (V4e white test light), and 30 Hz (cone) full-field ERG amplitudes were recorded for an average of 9.8 years in 113 patients with *RPGR* mutations. After censoring data to eliminate ceiling and floor effects, we used longitudinal regression to estimate mean rates of change and to compare these rates with those of a previously studied cohort of 134 patients with dominant retinitis pigmentosa due to *RHO* mutations, who were followed for an average of 8.9 years. Survival analysis was used to compare the age distribution of legal blindness in these two groups. To explain group differences in visual acuity, optical coherence tomograms were recorded in some patients to visualize central retinal structure.

Results. Mean annual exponential rates of decline for the patients with *RPGR* mutations were 4.0% for visual acuity, 4.7% for visual field area, and 7.1% for ERG amplitude. Each of these rates was significantly different from zero ($P < 0.001$). The rates of visual acuity and visual field loss were significantly faster than the corresponding rates in the *RHO* patients (1.6%, $P < 0.001$ and 2.9%, $P = 0.002$, respectively), whereas the rate of ERG amplitude loss was comparable to that in the *RHO* patients (7.7%, $P = 0.39$). The median age of legal blindness was 32 years younger in the *RPGR* patients than in the *RHO* patients, due primarily to loss of visual acuity rather than to loss of visual field. Loss of acuity in *RPGR* patients appeared to be associated with foveal thinning.

Conclusions. Patients with X-linked retinitis pigmentosa due to *RPGR* mutations lose visual acuity and visual field more rapidly than do patients with dominant retinitis pigmentosa due to *RHO* mutations. (*Invest Ophthalmol Vis Sci.* 2007;48:1298–1304) DOI:10.1167/iovs.06-0971

In retinitis pigmentosa, it is commonly thought that the X-linked form progresses most rapidly and that the dominant form progresses least rapidly, but this impression is primarily based on single visits and not on observing the same patients over time. In 1985 a longitudinal study showed that patients with dominant retinitis pigmentosa as a group were half as likely to lose cone electroretinogram (ERG) amplitude over a 3-year time interval as were patients with autosomal recessive, X-linked, and isolated disease combined.[1] However, the number of patients was too small and the follow-up too short in that study to consider similar comparisons with respect to loss of visual acuity and visual field area, which progress more slowly than loss of ERG amplitude, or to compare the X-linked form with other genetic types.

The discovery of the molecular bases for different forms of retinitis pigmentosa has allowed us and others to reclassify patients according to their responsible gene defects. We recently reported mean rates of decline in ocular function for a large cohort of patients with dominant retinitis pigmentosa due to mutations in the rhodopsin (*RHO*) gene.[2] In the present study we report mean rates of decline in a similar-sized cohort of patients with X-linked retinitis pigmentosa due to mutations in the retinitis pigmentosa GTPase regulator (*RPGR*) gene, the protein of which is expressed in the connecting cilia of cones as well as rods,[3] and compare these rates with those of patients with *RHO* mutations.

Methods

Patients

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School. We measured visual acuities, visual fields, and ERGs from 113 males (mean age at baseline: 26.1 years, age range at baseline, 5–61 years) with X-linked retinitis pigmentosa due to an *RPGR* mutation and at least 3 years of follow-up. The methods used to identify the *RPGR* mutations in these patients and the DNA sequences of the mutations have been reported.[4,5] The *RPGR* dataset was derived from the results of an average of 7.2 ocular examinations per patient performed from 1975 to 2005 with the same test conditions; follow-up ranged from 3 to 28 years with a mean of 9.8 years. The *RHO* dataset, derived from a previous study,[2] was also limited to patients with at least 3 years of follow-up. This yielded a sample of 134 patients (mean age at baseline: 36.0 years, age range at baseline: 8–66 years) who had been observed for 3 to 24 years, with an average follow-up of 8.9 years based on an average of 6.2 examinations per patient. The mean age at baseline of the patients with *RPGR* mutations was significantly younger than that of the patients with *RHO* mutations ($P < 0.001$).

Clinical Evaluation

The patients with *RPGR* mutations and those with *RHO* mutations underwent identical ocular examinations. We recorded best corrected visual acuity by using a projected Snellen chart and coded them in decimal form (e.g., 20/40 = 0.5). Kinetic visual fields were measured to the V4e white test light and to one or more smaller test lights in the Goldmann perimeter against the standard background of 31.5 apostilbs, bringing the test light from nonseeing to seeing areas. Fields were plotted with a digitizing tablet or scanned by custom software and

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Supported by National Eye Institute Grants EY00169, EY08683, and EY14104 and The Foundation Fighting Blindness.

Submitted for publication August 16, 2006; revised October 31, 2006; accepted January 23, 2007.

Disclosure: **M.A. Sandberg**, None; **B. Rosner**, None; **C. Weigel-DiFranco**, None; **T.P. Dryja**, None; **E.L. Berson**, None

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Investigative Ophthalmology & Visual Science, March 2007, Vol. 48, No. 3

TABLE 1. Baseline Ocular Function of Patients with *RPGR* Mutations in Exons 1 to 14

ID	Mutation*	Protein	Age (y)	VA† OD	VA† OS	VF‡ OD	VF‡ OS	ERG§ OD	ERG§ OS
5843	c.186G→A	Gly43Arg	26	20/50	20/40	1967	2410	0.45	0.49
410	c.187G→A	Gly43Glu	30	20/60	20/50	1473	405	NA	NA
6813	c.238G→T	Gly60Val	18	20/40	20/50	289	299	1.11	1.43
845	c.415delT	Leu119;Ter@131	19	20/100	20/400	NA	NA	2.7	2.7
6947	c.415delT	Leu119;Ter@131	30	20/60	20/50	NA	NA	0.11	0.11
3933	c.438A→G	Arg127Gly	19	20/200	20/60	87	280	NA	NA
7539	c.438A→G	Arg127Gly	25	20/50	20/40	2355	2464	0.02	0.09
6208	c.544_545delTT	Phe162;Ter@165	31	20/50	20/50	1120	2141	0.13	0.2
19673	c.664C→A	Ser202Ter	8	20/50	20/50	13371	13941	NA	6.28
5571	c.664C→A	Ser202Ter	27	20/50	20/60	3893	4079	NA	NA
116	c.806delC	Ala249;Ter@296	27	20/200	20/70	7625	9005	NA	NA
6004	c.896delT	Phe279;Ter@297	27	20/50	20/50	2626	3379	0.29	0.43
15587	c.897_901delCTTTT	Leu280;Ter@280	34	20/30	20/40	3603	3330	0.85	1.04
1053	c.928delA	Glu290;Ter@297	34	20/40	20/40	512	209	NA	NA
5784	c.964G→A	Cys302Tyr	33	20/70	20/80	3563	3622	0.58	0.56
19353	c.1039T→G	Leu327Ter	8	20/70	20/80	9533	9931	2.45	3.65
19351	c.1039T→G	Leu327Ter	9	20/50	20/40	11535	10512	3.3	2.6
6082	c.1151_1152insT	Ala365;Ter@376	24	20/40	20/30	2313	2166	0.05	0.06
582	c.1159delC	Pro367;Ter@380	46	20/60	20/100	308	245	0.27	0.14
3157	c.1366G→A	Gly436Asp	5	20/30	20/30	9985	0	8	8
1779	c.1366G→A	Gly436Asp	17	20/50	20/25	11527	9769	15	NA
1591	c.1366G→A	Gly436Asp	19	20/30	20/25	11608	10917	NA	NA
11730	c.1366G→A	Gly436Asp	47	20/200	20/100	4017	4624	1.93	2.38
7056	c.1435_1436delTC	Val459;Ter@461	27	20/30	20/40	2356	3220	0.6	0.8
2981	c.1435_1436delTC	Val459;Ter@461	31	20/30	20/25	3135	2925	NA	NA
5714	c.1641_1644delACAA	Thr528;Ter@531	33	20/70	20/50	2163	2396	0.22	0.19
3288	c.1806G→T	Glu583Ter	25	20/50	20/70	NA	NA	NA	NA
5955	IVS1+1G→A	Unknown	41	20/60	20/60	3408	6374	7.23	7.29
15433	IVS7-1G→A	Unknown	22	20/50	20/60	6022	8437	0.82	0.77
3044	IVS13-1G→A	Unknown	12	20/30	20/30	9966	8800	NA	NA
15521	IVS13-1G→A	Unknown	31	20/20	20/400	7228	6359	3.87	3.92
1560	IVS3-6T→A	Unknown	25	20/25	20/25	1991	1793	1.83	1.83
6737	IVS4_1G→C	Unknown	22	20/40	20/30	9435	9626	0.43	0.31
		Mean	26	20/45	20/46	4967	4789	2.27	1.97

NA, not available.

* Nucleotide positions in *RPGR* exons 1 to 14 are based on the study by Meindl et al.[15]

† Measured with a projected Snellen chart.

‡ Visual field area in deg^2 to the V4e white stimulus of the Goldmann perimeter (normal $\geq$ 11,399 deg^2).

§ ERG amplitude in μV to 30 Hz white full-field stimulation (normal $\geq$ 50 μV).

converted to areas in square degrees. Although a cartographic distortion arises from projecting the curved surface of the perimeter onto the flat visual field chart[6] and the projection of the visual field onto the retina is nonlinear based on a schematic eye,[7] most longitudinal studies of visual field progression in retinitis pigmentosa have not applied corrections to their chart data,[1,2,8–10] and we elected to do the same for consistency. We elicited full-field cone ERGs with 10-μs, 30-Hz flashes of white light (0.2 cd-s/m^2) after pupillary dilation, 45 minutes of dark adaptation, and having recorded responses in the dark to 0.5 Hz flashes of light. ERGs were monitored with a contact lens electrode on the topically anesthetized cornea and differentially amplified. Consecutive responses to 30-Hz flashes greater than 10 μV in amplitude were photographed from the screen of an oscilloscope or digitized and quantified by computer. Smaller responses were digitized, smoothed with a band-pass filter, and averaged. Waveforms in response to 30-Hz flashes were quantified with respect to trough-to-peak amplitudes, and amplitudes $<$0.05 μV, considered nondetectable, were recoded as 0.05 μV. In this study, we limited our analyses to the V4e white test light for measuring visual fields and to 30-Hz white flashes for eliciting ERGs, because only these conditions of testing provided us with sufficiently large data sets to estimate rates of change with high precision.

As part of a separate program,[11] we had recorded optical coherence tomograms (OCTs) from 5 of the patients with *RPGR* mutations (age range, 19–47 years) and from 10 of the patients with *RHO* mutations (age range, 20–52 years). The *RPGR* patients had visual acuities of 20/30 to 20/200, and the *RHO* patients had visual acuities of 20/20 to 20/60 (excluding an eye of one patient with a history of deep amblyopia). We evaluated these tomograms to search for a structural basis for visual acuity differences in these two groups.

Statistical Analyses

For estimating mean rates of change, we censored visual acuities of 20/20, except those that followed a lower value, to minimize a ceiling effect, because on our coding sheet we had constrained Snellen visual acuities to be $\leq$20/20. To minimize floor effects, we also censored patients with baseline visual acuities $<$20/100 and follow-up data after visual acuity declined to $<$20/100. For patients who became aphakic or pseudophakic in either eye at follow-up, those follow-up visits were excluded from visual acuity analyses. We also censored baseline visual field areas $<$78 deg^2 (i.e., equivalent to a diameter of 10°) and follow-up data after the first occurrence of an area $<$78 deg^2 to minimize floor effects. To minimize floor effects, we censored baseline ERG amplitudes $<$0.68 μV and follow-up data after the amplitude decreased to $<$0.34 μV. The censoring criteria were those applied in a previous study of patients with dominant *RHO* mutations.[2] After applying these criteria, we eliminated patients from a given analysis if their residual follow-up was $<$3 years.

We converted all measures of ocular function to natural logarithms, because an exponential model has been shown to be optimal for evaluating cell loss over time in animal models of retinitis pigmen-

TABLE 2. Baseline Ocular Function of Patients with *RPGR* Mutations in ORF15

ID	Mutation*	Protein	Age (y)	VA† OD	VA† OS	VF‡ OD	VF‡ OS	ERG§ OD	ERG§ OS
7273	g.ORF15+82_83insA	ORF15Asn27;Ter@43	13	20/30	20/40	3734	4151	0.6	0.6
15396	g.ORF15+327A→T	ORF15Lys109Ter	25	20/30	20/30	8440	8051	2.59	2.51
15370	g.ORF15+369G→T	ORF15Glu123Ter	34	20/80	20/80	4536	3952	5.59	4.4
6045	g.ORF15+423G→T	ORF15Glu141Ter	31	20/70	20/200	834	305	0.21	0.27
6820	g.ORF15+465G→T	ORF15Glu155Ter	28	20/40	20/40	2094	3293	0.44	0.59
19848	g.ORF15+465G→T	ORF15Glu155Ter	34	20/40	20/50	2686	3471	0.77	0.86
7730	g.ORF15+481_484delGAGA	ORF15Arg160;Ter@229	16	20/40	20/40	10076	12254	0.24	0.22
7258	g.ORF15+481_484delGAGA	ORF15Arg160;Ter@229	17	20/50	20/50	9710	9710	0.2	0.13
3554	g.ORF15+483_484delGA	ORF15Glu161;Ter@183	18	20/40	20/40	NA	NA	NA	NA
6977	g.ORF15+483_484delGA	ORF15Glu161;Ter@183	24	20/30	20/25	3099	3440	3.91	3.28
6219	g.ORF15+483_484delGA	ORF15Glu161;Ter@183	33	20/60	20/400	3882	3493	1.11	0.51
2482	g.ORF15+499_502delAGGA	ORF15Lys166;Ter@229	22	20/30	20/40	8020	7086	NA	NA
7344	g.ORF15+507G→T	ORF15Glu169Ter	17	20/25	20/20	9978	8544	1.3	1.8
5667	g.ORF15+507G→T	ORF15Glu169Ter	19	20/20	20/25	12961	11504	4.21	5.43
5654	g.ORF15+507G→T	ORF15Glu169Ter	30	20/400	20/40	1198	1552	0.4	0.4
6197	g.ORF15+507G→T	ORF15Glu169Ter	33	20/40	20/40	NA	NA	NA	NA
7073	g.ORF15+517_518delAG	ORF15Glu172;Ter@183	24	20/40	20/40	1655	2364	0.32	0.23
3389	g.ORF15+614_615delAA	ORF15Lys201;Ter@248	14	20/70	20/60	9936	11556	NA	NA
7402	g.ORF15+614_615delAA	ORF15Lys201;Ter@248	24	20/40	20/200	2652	1939	0.24	0.28
5740	g.ORF15+614_615delAA	ORF15Lys201;Ter@248	34	20/60	20/400	5322	3884	2.86	2.71
5849	g.ORF15+650_653delAGAG	ORF15Thr216;Ter@229	26	20/100	20/70	4868	5128	0.24	0.18
3794	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	26	20/70	20/30	NA	NA	NA	NA
3248	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	14	20/30	20/30	NA	NA	NA	24
5935	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	16	20/25	20/30	2883	2332	0.59	0.59
11496	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	19	20/40	20/30	11851	11460	3.5	3.64
6631	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	19	20/30	20/80	2341	2604	1.6	1.53
125	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	21	20/30	20/40	NA	NA	NA	NA
15290	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	26	20/100	20/80	4899	6706	2.36	3.9
5757	g.ORF15+652_653delAG	ORF15Glu217;Ter@248	31	20/70	20/80	3328	4165	2.4	1.25
6857	g.ORF15+659_660delAG	ORF15Arg219;Ter@248	15	20/30	20/30	12003	12491	1.2	2
6772	g.ORF15+659_660delAG	ORF15Arg219;Ter@248	34	20/70	20/60	2717	2591	0.72	0.54
14309	g.ORF15+670_671delAA	ORF15Lys223;Ter@248	8	20/30	20/30	8874	8360	6.09	6.16
1924	g.ORF15+670_671delAA	ORF15Lys223;Ter@248	21	20/30	20/40	6800	6024	17	17
14066	g.ORF15+673_674delAG	ORF15Glu224;Ter@248	16	20/30	20/20	6936	10409	13	13
7364	g.ORF15+673_674delAG	ORF15Glu224;Ter@248	29	20/50	20/40	616	1139	0.08	0.16
1886	g.ORF15+673_674delAG	ORF15Glu224;Ter@248	31	20/100	20/200	NA	NA	NA	NA
156	g.ORF15+673_674delAG	ORF15Glu224;Ter@248	33	20/400	20/400	NA	NA	NA	NA
13290	g.ORF15+684G→T	ORF15Glu228Ter	8	20/70	20/70	8460	11008	1.47	1.05
5656	g.ORF15+689_692delAGAG	ORF15Val229;Ter@234	21	20/400	20/400	5338	5443	NA	NA
7038	g.ORF15+689_692delAGAG	ORF15Val229;Ter@234	30	20/70	20/70	3997	3912	1.75	1.37
14362	g.ORF15+738G→T	ORF15Glu246Ter	22	20/70	20/80	692	741	0.09	0.09
15438	g.ORF15+740_741delGG	ORF15Glu246;Ter@248	7	20/50	20/50	NA	NA	4.41	3.5
2554	g.ORF15+746delT	ORF15Gly248;Ter@503	31	20/60	20/50	6787	7166	NA	NA
1175	g.ORF15+752_753delGG	ORF15Gly250;Ter@492	19	20/30	20/50	6015	6485	NA	NA
6154	g.ORF15+763_767delAAGGG	ORF15Glu254;Ter492	20	20/40	20/40	7363	5978	2.13	2.37
1887	g.ORF15+818_819delAG	ORF15Lys272;Ter@492	17	20/40	20/30	NA	NA	0.3	0.3
4025	g.ORF15+818_819delAG	ORF15Lys272;Ter@492	22	20/50	20/50	1785	739	NA	NA
1888	g.ORF15+818_819delAG	ORF15Lys272;Ter@492	29	20/40	20/40	NA	NA	NA	1.3
2964	g.ORF15+818_819delAG	ORF15Lys272;Ter@492	54	HM	20/200	NA	NA	NA	NA
5987	g.ORF15+872_873insA	ORF15Gly291;Ter@492	27	20/70	20/200	4370	4848	NA	NA
5927	g.ORF15+897G→T	ORF15Glu299Ter	21	20/30	20/30	3202	3893	5.99	6.07
7983	g.ORF15+902_903delGG	ORF15Gly300;Ter@492	8	20/25	20/25	12014	9532	2.17	2.3
6471	g.ORF15+902_903delGG	ORF15Gly300;Ter@492	31	20/50	20/100	6014	5042	2.01	2.22
15596	g.ORF15+872_873insA	ORF15Gly291;Ter@492	27	20/50	20/40	NA	NA	2.24	2.7
43	g.ORF15+906_909delGGAG	ORF15Gly302;Ter@503	12	20/40	20/200	NA	NA	NA	NA
15133	g.ORF15+926_927delGG	ORF15Gly308;Ter@492	32	20/50	20/60	NA	NA	NA	NA
1781	g.ORF15+954G→T	ORF15Glu318Ter	40	CF@10ft	CF@5ft	NA	NA	NA	NA
14443	g.ORF15+954G→T	ORF15Glu318Ter	61	CF@10ft	CF@5ft	1986	1444	NA	NA
5996	g.ORF15+961_962delAA	ORF15Glu320;Ter492	29	20/60	20/40	4290	4727	2.63	2.02
11425	g.ORF15+962-963insCCTC	ORF15Glu321;Ter@492	40	20/60	20/100	361	363	0.49	0.28
1158	g.ORF15+963G→T	ORF15Glu321Ter	30	20/60	20/60	1390	1665	NA	NA
15908	g.ORF15+977_978delGG	ORF15Gly325;Ter@492	42	20/200	20/100	NA	NA	2.55	2.66
5923	g.ORF15+1010_1011delGG	ORF15Gly336;Ter@492	31	20/50	20/50	671	566	0.25	0.17
6480	g.ORF15+1047G→T	ORF15Glu349Ter	21	20/40	20/60	3560	3593	1.76	1.08
6184	g.ORF15+1113delG	ORF15Glu371;Ter@503	18	20/40	20/50	5774	6889	0.08	0.13
6719	g.ORF15+1146delG	ORF15Glu382;Ter@503	18	20/50	20/40	5514	9059	0.78	0.49
6079	g.ORF15+1146delG	ORF15Glu382;Ter@503	37	20/50	20/70	6783	5170	3.14	2.68
15805	g.ORF15+1184_1185delGG	ORF15Gly394;Ter@492	15	20/80	20/60	7622	8933	7.2	7.3

(*continues*)

TABLE 2. (*continued*). Baseline Ocular Function of Patients with *RPGR* Mutations in ORF15

ID	Mutation*	Protein	Age (y)	VA† OD	VA† OS	VF‡ OD	VF‡ OS	ERG§ OD	ERG§ OS
5852	g.ORF15+1184_1185delGG	ORF15Gly394;Ter@492	18	20/50	20/60	4704	9035	1.5	1.4
5741	g.ORF15+1191delG	ORF15Glu397;Ter@503	41	20/40	20/40	4864	4832	4.38	3.02
3892	g.ORF15+1254_1257delGGAG	ORF15Gly418;Ter@503	26	CF@10ft	20/80	9681	9090	NA	NA
7748	g.ORF15+1254_1257delGGAG	ORF15Gly418;Ter@503	26	20/70	20/80	9936	9355	0.7	1.4
3894	g.ORF15+1254_1257delGGAG	ORF15Gly418;Ter@503	28	20/50	20/60	9391	9138	NA	NA
7843	g.ORF15+1254_1257delGGAG	ORF15Gly418;Ter@503	35	20/200	20/400	7347	8452	1.62	2.16
15151	g.ORF15+1254_1257delGGAG	ORF15Gly418;Ter@503	40	20/400	20/400	NA	NA	4.2	5.6
5754	g.ORF15+1258_1259delAG	ORF15Glu419;Ter@492	25	20/200	20/50	609	930	0.06	0.12
7555	g.ORF15+1339_1340delAG	ORF15Glu446;Ter@493	45	20/80	20/30	7288	6602	13	13
6889	g.ORF15+1339delA	ORF15Glu446;Ter@503	20	20/30	20/25	15537	13333	6.9	7.38
6635	g.ORF15+1339delA	ORF15Glu446;Ter@503	25	20/40	20/50	619	1065	0.14	0.12
14072	g.ORF15+1343_1344delGG	ORF15Gly447;Ter@493	47	20/200	20/200	12026	12153	3.92	4.2
		Mean	26	20/49	20/51	5634	5796	2.66	2.99

CF, count fingers; HM, hand motions. NA, not available.

* Nucleotide positions in ORF15 are based on the study by Vervoort et al.[16]

† Measured with a projected Snellen chart.

‡ Visual field area in deg^2 to the V4e white stimulus of the Goldmann perimeter (normal $\geq$ 11,399 deg^2).

§ ERG amplitude in microvolts to 30 Hz white full-field stimulation (normal $\geq$ 50 μV).

tosa,[12] provides a good fit for describing short-term disease progression in patients with retinitis pigmentosa,[2] and has been used in several longitudinal studies of retinitis pigmentosa.[1,2,8–10,13,14] Repeated-measures longitudinal regression (performed with PROC MIXED of SAS, ver. 9; SAS Institute, Cary, NC) was used to estimate the mean rate of change for each outcome measure, based on the average $\log_e$ value for both eyes at each visit (when data for both eyes were available). By including terms for genotype (i.e., *RPGR* versus *RHO* mutation) and the cross-product of time $\times$ genotype, we compared mean slopes in patients with *RPGR* mutations versus mean slopes in patients with *RHO* mutations. We also used longitudinal regression to compare the mean rates of progression in patients with *RPGR* mutations in exons 1 to 14 (n = 33) with the mean rates in patients who had *RPGR* mutations in open reading frame (ORF) 15 (n = 80), because a previous analysis had suggested differences in ocular function between these two groups based on single visits.[5]

We used the commercial software (PROC LIFEREG of SAS) to fit a Weibull function to survival data and compare the age distribution of legal blindness in patients with *RPGR* mutations to the corresponding distribution in patients with *RHO* mutations. These plots provide a visualization of the long-term course of disease, and the model allows inclusion of left-censored data (i.e., a patient failing at baseline) and right-censored data (i.e., a patient not failing during follow-up) as well as interval-censored data (i.e., a patient failing between exams occurring at ages $x1$ and $x2$). For this purpose, we applied failure criteria (i.e., a visual acuity $\leq$20/200 or a visual field area $\leq$314 deg^2 in one eye and a visual acuity $\leq$20/200 or a visual field area $\leq$314 deg^2 in the fellow eye) to the entire dataset. The area of 314 deg^2 corresponds to an equivalent diameter of 20° (i.e., a criterion for legal blindness) and was used in lieu of measuring the linear extent of each remaining visual field directly from charts. We also used a visual acuity $\leq$20/200 alone and a visual field area $\leq$314 deg^2 alone as failure criteria, to determine which was the critical factor that led to legal blindness in each group.

RESULTS

Baseline Ocular Function

Tables 1 and 2 list the baseline raw data and mean values for the *RPGR* patients with mutations in exons 1 to 14 and with ORF15 mutations, respectively. None of the mean values in one group is significantly different from the corresponding mean value in the other group.

Mean Rates of Change

Table 3 shows the mean annual $\log_e$ rates of change in the patients with *RPGR* mutations, with standard errors and significance levels. The mean $\log_e$ values correspond to mean annual exponential rates of decline of 4.0% for Snellen visual acuity, 4.7% for visual field area to the V4e test light, and 7.1% for cone ERG amplitude to 30-Hz flashes. In comparison, the *RHO* patients had a mean annual exponential rate of visual acuity decline (1.6%) and a mean annual exponential rate of visual field decline (2.9%) that were slower than the corresponding rates in the patients with *RPGR* mutations ($P < 0.001$ and $P = 0.002$, respectively). In contrast, the *RHO* patients had a mean annual exponential rate of decline in ERG amplitude (7.7%) that was not significantly different from that of the *RPGR* patients ($P = 0.39$).

When we divided our patients with *RPGR* mutations into those with mutations in exons 1 to 14 and those with mutations in ORF15, we found a significant group difference in the mean annual exponential rates of decline in ERG amplitude (9.5% versus 6.3%, respectively; $P = 0.005$), but no significant difference in the rates of decline in visual acuity (3.4% versus 4.3%, respectively; $P = 0.17$) or visual field (4.9% versus 4.6%, respectively; $P = 0.78$).

Median Age to Reach Legal Blindness

We found a significant effect of genotype on the age distribution for legal blindness ($P < 0.001$). Figure 1 shows that our patients with *RPGR* mutations reached legal blindness, based on loss of acuity and/or field, at a median age (45 years) that was 32 years younger than that of our patients with *RHO*

TABLE 3. Annual Rates of Change in Patients with *RPGR* Mutations

Ocular Function	n*	Mean ± SEM†	P†
$\log_e$ visual acuity	93	−0.041 ± 0.003	<0.001
$\log_e$ visual field area	102	−0.048 ± 0.004	<0.001
$\log_e$ ERG amplitude	60	−0.074 ± 0.006	<0.001

* After censoring data to minimize ceiling and floor effects and preserve a follow-up $\geq$ 3 years.

† Calculated by longitudinal regression using PROC MIXED of SAS.

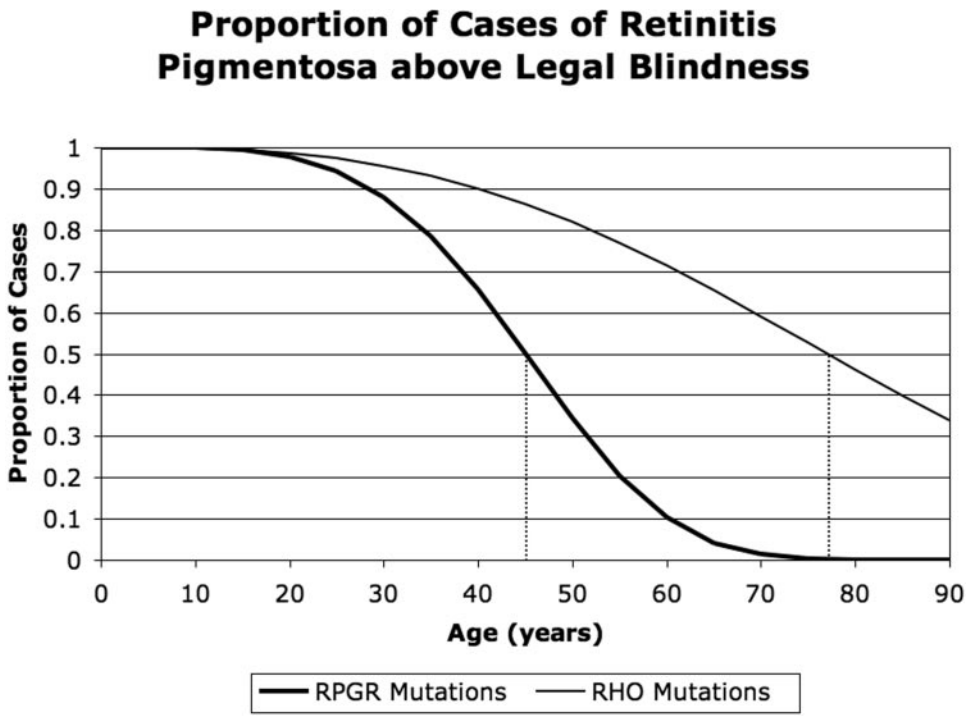

FIGURE 1. Weibull plot survival analysis for legal blindness (i.e., loss of acuity and/or field) by genotype. The effect of genotype was significant (Wald χ^2 test, $P < 0.001$). *Vertical lines*: median age of legal blindness in patients with *RPGR* mutations (*left*) and in patients with *RHO* mutations (*right*).

mutations (77 years). Figure 2 shows that the development of legal blindness was driven primarily by visual acuity loss in the patients with *RPGR* mutations and by visual field loss in the patients with *RHO* mutations. That is, in the patients with *RPGR* mutations, the survival curve based on a visual acuity of 20/200 or less is shifted to younger ages compared with the survival curve based on a visual field area of 314 deg^2 or less. In contrast, the visual field survival curve is shifted to younger ages compared with the visual acuity survival curve of the patients with *RHO* mutations.

Figure 2 also shows that, although the time course for surviving visual acuity was markedly different by genotype, the time course for surviving visual field was not significantly different in the two groups of patients. Because our clinical impression has been that patients with X-linked retinitis pigmentosa are left with a small central island of vision at a younger age than patients with dominant retinitis pigmentosa, we repeated the visual field survival comparison after subtracting peripheral islands from field area and then censoring baseline field areas >4915 deg^2, to exclude fields with large peripheral areas connected by a narrow bridge to the central field. We found a significant effect of genotype on the age distribution for retaining central field ($P < 0.001$, Fig. 2). The median age for central field area decreasing to 314 deg^2 or less was 22 years younger in the *RPGR* patients (37 years) than in the *RHO* patients (59 years).

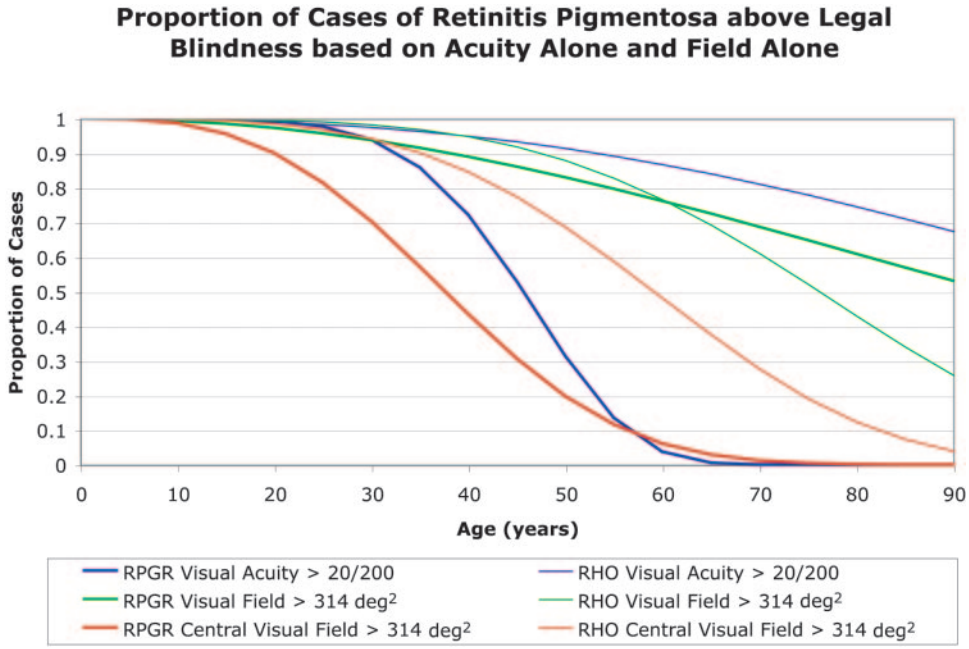

FIGURE 2. Weibull plot survival analysis for a visual acuity >20/200 (*blue curves*) or a visual field area >314 deg^2 (i.e., an equivalent diameter of 20°, *green curves*) by genotype. Visual field survival is also shown for the central field, excluding peripheral islands (*red curves*). The effect of genotype was significant for visual acuity ($P < 0.001$) and for central field ($P < 0.001$), but not for total field ($P = 0.29$).

TABLE 4. Visual Acuity and Central Foveal Thickness by Genotype in Retinitis Pigmentosa

Genotype	ID	Age (y)	Visual Acuity*	Central Foveal Thickness (μm)*
RHO	19400	26	20/20	156
	15594	39	20/20	187
	19785	40	20/25	172
	19173	41	20/30	165
	19582	43	20/20	173
RPGR	14309	19	20/30	134
	15396	32	20/44	147.5
	11496	33	20/114	37
	15133	38	20/89	83.5
	1888	47	20/55	117

* Mean of both eyes. Lower norm for central foveal thickness = 118 μm for these conditions of testing.[11]

Optical Coherence Tomography

Five of the 10 *RHO* patients with available OCTs had reduced visual acuity associated with macular cysts and were not considered further. Of the remaining patients with tomograms, the five with *RHO* mutations had a mean visual acuity of 20/22 and the five with *RPGR* mutations had a mean visual acuity of 20/53 (Table 4). This difference was significant ($P = 0.002$). Their mean retinal thicknesses at the foveal center were 171 and 104 μm, respectively. The thickness in the *RHO* patients is similar to the normal mean thickness for our test system (167 μm),[11] and that in the *RPGR* patients is significantly smaller than that in the *RHO* patients (*t*-test for unequal variances, $P = 0.03$). Figure 3 shows a tomogram from a 40-year-old *RHO* patient with a visual acuity of 20/25 and from a 38-year-old *RPGR* patient with a visual acuity of 20/100. The patient with the *RHO* mutation had a normal retinal thickness profile, whereas the patient with the *RPGR* mutation had a broad foveal depression with attenuation of the outer nuclear layer centrally, indicating loss of central foveal cones.

DISCUSSION

The present study, based on data from two large cohorts observed for an average of 8 and 9 years, shows that patients with retinitis pigmentosa due to *RPGR* mutations lost Snellen visual acuity at more than twice the mean rate of patients with retinitis pigmentosa due to *RHO* mutations. Our survival analyses over the long term showed that the median age of legal blindness was much younger age in patients with *RPGR* mutations than in patients with *RHO* mutations. Our data also showed that becoming legally blind was due primarily to loss of visual acuity in RPGR patients and to loss of visual field in RHO patients.

OCT recordings revealed that the difference in mean visual acuity between these two groups may be attributable to photoreceptor loss. The tomograms of one *RPGR* patient showed a broad thinning of the fovea resembling that in the tomograms of patients with Stargardt's disease[17] or occult macular dystrophy.[18] When visual acuity was reduced in patients with *RHO* mutations, it tended to be associated with macular cysts. Study of OCTs from additional *RHO* patients and *RPGR* patients who have reduced visual acuity will reveal whether these features are characteristic of these two groups.

We also found that patients with *RPGR* mutations lost visual field area to the V4e stimulus at a mean rate that was approximately 50% faster than that in patients with *RHO* mutations and were left with a central island of vision ≤20° at a younger median age than the *RHO* patients. This result suggests that the faster loss of visual acuity by the *RPGR* patients may be a consequence of their faster loss of central field, consistent with a significant correlation between visual acuity and central visual field diameter in retinitis pigmentosa.[19] However, the two groups had similar age distributions for retaining 20° of total visual field and had nearly identical mean rates of progression of the full-field cone ERG, which derives mostly from the peripheral retina.

In a previous study based on single visits with adjustment for differences in age, we reported that patients with *RPGR* mutations in exons 1 to 14 had a borderline smaller mean visual field area ($P = 0.04$) and mean cone ERG amplitude ($P = 0.06$) than did patients with *RPGR* mutations in ORF15,[5] suggesting that the former group had more severe disease at a given age than did the latter group. In the present study we evaluated whether mean rates of disease progression were different in these two groups. We found that patients with exon 1 to 14 mutations lost ERG amplitude 50% faster than did

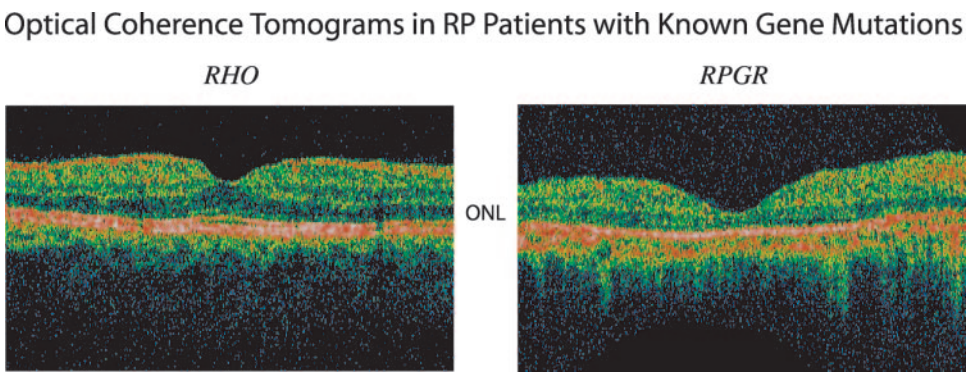

FIGURE 3. Tomograms subtending 20° (Stratus High-resolution Optical Coherence Tomographer [OCT3], Carl Zeiss Meditec, Inc., Dublin, CA) from the right eye of a 40-year-old woman with dominant retinitis pigmentosa due to an *RHO* mutation (Pro23His) and visual acuity of 20/25 (*left*) and from the right eye of a 38-year-old man with X-linked retinitis pigmentosa due to an *RPGR* mutation (ORF15Gly308;Ter@492) and visual acuity of 20/100 (right). ONL, outer nuclear layer.

patients with ORF15 mutations, whereas visual acuity and visual field area declined comparably in the two groups. We, therefore, conclude that *RPGR* mutations in exons 1 to 14 tend to cause a more rapid loss of peripheral cone retinal function than do mutations in ORF15.

Acknowledgments

The authors thank Terri L. McGee for help in compiling the list of *RPGR* mutations.

References

1. Berson EL, Sandberg MA, Rosner B, et al. Natural course of retinitis pigmentosa over a three-year interval. *Am J Ophthalmol*. 1985;99: 240–251.
2. Berson EL, Rosner B, Weigel-DiFranco C, Dryja TP, Sandberg MA. Disease progression in patients with dominant retinitis pigmentosa and rhodopsin mutations. *Invest Ophthalmol Vis Sci*. 2002;43: 3027–3036.
3. Hong D, Pawlyk BS, Shang J, et al. A retinitis pigmentosa GTPase regulator (RPGR)-deficient mouse model of X-linked retinitis pigmentosa (RP3). *Proc Natl Acad Sci USA*. 2000;97:3649–3654.
4. Sharon D, Bruns GAP, McGee TL, Sandberg MA, Berson EL, Dryja T. X-linked retinitis pigmentosa: mutation spectrum of the *RPGR* and *RP2* genes and correlation with visual function. *Invest Ophthalmol Vis Sci*. 2000;41:2712–2721.
5. Sharon D, Sandberg MA, Rabe VW, Stillberger M, Dryja TP, Berson EL. *RP2* and *RPGR* mutations and clinical correlations in patients with X-linked retinitis pigmentosa. *Am J Hum Genet*. 2003;73: 1131–1146.
6. Kirkham TH, Meyer E. Visual field area on the Goldmann hemispheric perimeter surface: correction of cartographic errors inherent in perimetry. *Curr Eye Res*. 1981;1:93–99.
7. Drasdo N, Fowler CW. Non-linear projection of the retinal image in a wide-angle schematic eye. *Br J Ophthalmol*. 1974;58:709–714.
8. Holopigian K, Greenstein V, Seiple W, Carr RE. Rates of change differ among measures of visual function in patients with retinitis pigmentosa. *Ophthalmology*. 1996;103:398–405.
9. Grover S, Fishman GA, Anderson RJ, Alexander KR, Derlacki DJ. Rate of visual field loss in retinitis pigmentosa. *Ophthalmology*. 1997;104:460–465.
10. Iannaccone A, Kritchevsky SB, Ciccarelli ML, et al. Kinetics of visual field loss in Usher Syndrome type II. *Invest Ophthalmol Vis Sci*. 2004;45:784–792.
11. Sandberg MA, Brockhurst RJ, Gaudio AR, Berson EL. The association between visual acuity and central retinal thickness in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2005;46:3349–3354.
12. Clarke G, Collins RA, Leavitt BR, et al. A one-hit model of cell death in inherited neuronal degenerations. *Nature*. 2000;406:195–199.
13. Massof RW, Dagnelie G, Benzschawel T, Palmer RW, Finkelstein D. First order dynamics of visual field loss in retinitis pigmentosa. *Clin Vis Sci*. 1990;5:1–26.
14. Birch DG, Anderson JL, Fish GE. Yearly rates of rod and cone functional loss in retinitis pigmentosa and cone-rod dystrophy. *Ophthalmology*. 1999;106:258–268.
15. Meindl A, Dry K, Herrmann K, et al. A gene (RPGR) with homology to the RCC1 guanine nucleotide exchange factor is mutated in X-linked retinitis pigmentosa (RP3). *Nat Genet*. 1996;13:35–42.
16. Vervoort T, Lennon A, Bird AC, et al. Mutational hot spot within a new RPGR exon in X-linked retinitis pigmentosa. *Nat Genet*. 2000; 25:462–466.
17. Ergun E, Hermann B, Wirtitsch M, et al. Assessment of central visual function in Stargardt's disease/fundus flavimaculatus with ultrahigh-resolution optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2005;46:310–316.
18. Brockhurst RJ, Sandberg MA. Optical coherence findings in occult macular dystrophy. *Am J Ophthalmol*. 2007;143:516–518.
19. Madreperla SA, Palmer RW, Massof RW, Finkelstein D. Visual acuity loss in retinitis pigmentosa: relationship to visual field loss. *Arch Ophthalmol*. 1990;108:358–361.