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CLINICAL STUDY

Phenotypic progression in X-linked retinitis pigmentosa secondary to a novel mutation in the *RPGR* gene

A Al-Maskari[1], A O'Grady[2], B Pal[1] and M McKibbin[1]

Abstract

Purpose **To report phenotypic progression for a novel mutation in the *RPGR* gene causing X-linked retinitis pigmentosa (RP), and describe the phenotype in affected males and females**

Methods **Bidirectional fluorescent sequencing analysis was used to screen for mutations in *RPGR*. Five affected males and eight affected females from two English families underwent refraction, ETDRS visual acuity, OCT imaging, and Goldmann visual field testing.**

Results **DNA analysis identified a novel c.350G>A sequence change in exon 5 of *RPGR*. The change segregated with disease in both families. For affected males there was a significant correlation between age and visual acuity ($r=-0.91$, $P=0.034$), and a non-significant correlation between age and visual field area ($r=-0.56$, $P=0.4$). For affected females, there was a significant correlation between age and visual acuity ($r=-0.8$, $P=0.018$), and between age and visual field area ($r=-0.94$, $P=0.005$). All affected females were highly myopic. No correlation between retinal thickness, and either age or sex was noted.**

Conclusion **This novel mutation in *RPGR* causes X-Linked RP with complete penetrance in males and females. Affected females are highly myopic but retain better visual function than affected males. The phenotypic data can be used to provide a mutation-specific visual prognosis, and may also help recognition of the genotype.**

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Keywords: retinitis pigmentosa; X-linked; RPGR; mutation; phenotype

Introduction

X-Linked retinitis pigmentosa (RP) is the least common, but most severe form of RP. In this study, we report phenotypic progression for a novel mutation in exon 5 of *RPGR*, which causes X-linked RP with complete penetrance, and describe the phenotypic progression in affected males and females.

Methods

Molecular genetic analysis was performed on two English families with a clinical diagnosis of X-linked dominant RP at the National Genetic Reference Laboratory in Manchester, UK (Figure 1). To report the natural history of the phenotype, affected males and females underwent refraction, ETDRS visual acuity, OCT imaging, and Goldmann visual field testing. Data is presented for the right eye unless the right eye had significant co-pathology. Multivariate analysis of covariance was used to test the association of age and sex for each phenotypic variable.

Results

Bidirectional fluorescent sequencing analysis identified the novel sequence change c.350G>A (p.Gly117Glu) at position 117 in exon 5 of *RPGR*.[1] The change segregated with disease in both families, being present in eight affected cases and absent in three unaffected relatives. This glycine residue is conserved across a number of species, and *in silico* functional

[1]Department of Ophthalmology, St James's University Hospital, Leeds, UK

[2]National Genetics Reference Laboratory, St Mary's Hospital, Manchester, UK

Correspondence: M McKibbin, Department of Ophthalmology, St James's University Hospital, Beckett Street, Leeds, West Yorkshire, LS9 7TF, UK. Tel: +0113 206 6429; Fax: +0113 206 4578. E-mail: martin.mckibbin@leedsth.nhs.uk

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analysis suggests that substitution of glycine at residue 117 to glutamic acid is predicted to have a negative effect on the *RPGR* protein.

Age at examination ranged from 15 to 58 years in the five affected males and 15 to 67 years in the eight affected females (Table 1).

Affected males had refraction from +0.25 D to −10.00 D, ETDRS visual acuity from 75 to 0 letters, foveal thickness from 117 to 224 μm, and V4e Goldmann field area from 11747 mm^2 to 0 mm^2. There was a significant correlation between age and visual acuity ($r=-0.91$, $P=0.034$), and a non-significant correlation between age and visual field area ($r=-0.56$, $P=0.4$) (Figure 2).

Affected females had refraction from −7.00 D to −20.00 D, ETDRS visual acuity from 75 to 55 letters, foveal thickness from 144 to 212 μm, and V4e Goldmann field area from 15778 mm^2 to 5072 mm^2 There was a significant correlation between age and visual acuity ($r=-0.8$, $P=0.018$), and between age and visual field area ($r=-0.94$, $P=0.005$).

A non-significant trend was observed for affected females to have better visual acuity and field, but to be more myopic than affected males. No association with age or sex was observed for foveal thickness.

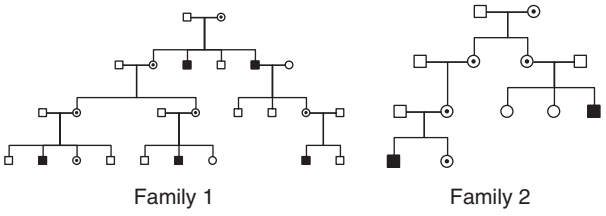

Figure 1 Pedigrees of the two X-linked RP families.

Discussion

RPGR mutations are estimated to cause 15–20% of all cases of RP, more than any other single RP locus.[2] Traditionally, most *RPGR* mutations would be considered to be recessive with clinically normal female carriers or heterozygotes. However, some X-linked mutations have a dominant effect with an abnormal phenotype in heterozygous females. For *RPGR*, this high penetrance in males and females cannot be accounted for by skewed inactivation of the X-chromosome, and seems to be most common with truncating mutations, particularly in exon ORF15.[3,4] In this study, we have shown that X-linked dominant RP can also be the result of a missense mutation in exon 5 of *RPGR*.

Heterozygous females in X-linked RP families may have no symptoms, but almost 50% may have either a tapetal reflex in the macula or peripheral pigmentary change.[2] However, as with other X-linked diseases, some females have symptoms and signs of RP, and are better regarded as being affected, as opposed to being carriers.[5] In these two families, complete penetrance was seen in both males and females. Expressivity in heterozygous females was severe, but with later onset loss of acuity and visual field than affected hemizygous males. Although visual acuity remained relatively good into the seventh decade, visual field showed a progressive deterioration with age. The most striking phenotypic

Table 1 Phenotypic data for the right eye

Number	*Sex*	*Age*	*Refraction (D)*	*ETDRS letter score*	*Foveal thickness (micron)*	*V4e field area (mm^2)*
Family 1						
1	M	58	−2.5[a]	0	NA	0
2	M	15	0.25	60	224	11747
3	M	19	−6	75	120	198
4	F	33	−7	73	212	11843
5	F	15	−14	70	162	15778
6	F	67	−11.5	55	149	NA
7	F	44	−20	75	144	5072
8	F	45	−20	70	NA	NA
Family 2						
9	M	25	−10	68	117	11132
10[b]	M	38	NA	55	190	NA
11[c]	F	44	−15	67	184	11008
12	F	66	−8.5	55	145	1212
13	F	22	−19	74	147	14263

NA, not available.
[a]Refraction value was at the age of 28.
[b]Pseudophakic.
[c]Data presented for the left eye as the right eye was amblyopic.

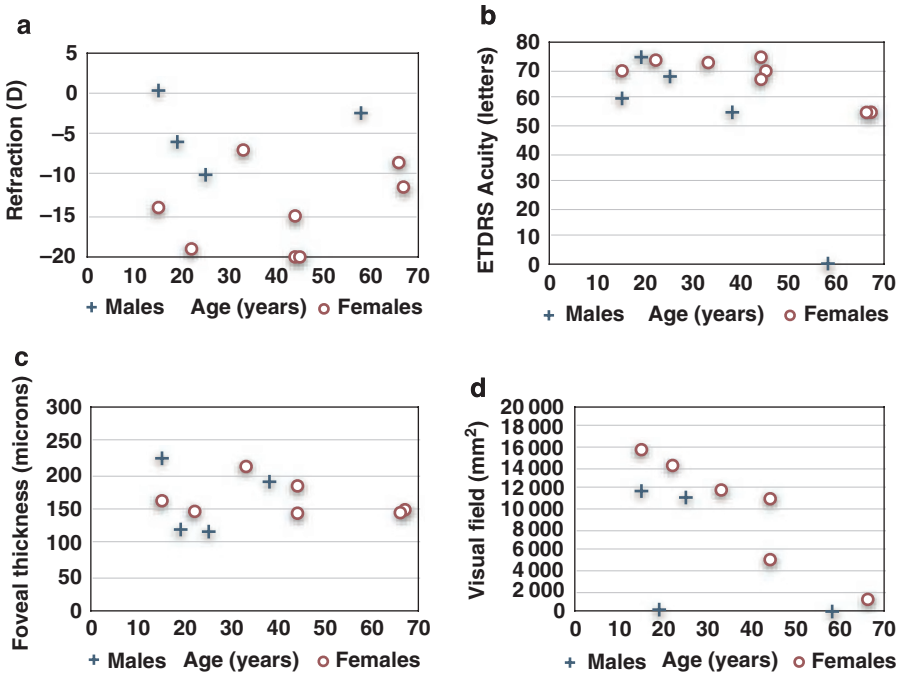

Figure 2 (a) Refraction *vs* age; (b) visual activity *vs* age; (c) foveal thickness *vs* age; (d) visual field *vs* age.

feature in affected females was high myopia, with mean refractive error being −14.38 D in females and −4.56 D in males. This feature was noted before either symptoms or signs of retinal degeneration, and may be the earliest and most reliable guide to the affected female status in X-linked dominant RP, its presence implying a mutation in the *RPGR* gene.[2,3] Heterozygous females had bone spiculation in the mid-peripheral retina. No tapetal reflex was seen and the macula was grossly normal.

Earlier reports have suggested that RP secondary to ORF15 mutations may have a more severe phenotype than RP secondary to mutations elsewhere in the *RPGR* gene.[6,7] In this study, there was a trend for both visual acuity and visual field to deteriorate with age in both males and females. Despite the small number of subjects, the association was often statistically significant. Limited longitudinal acuity and field data for individuals was in keeping with the pooled trends. This age-related progression must be noted when any comparison is made between the phenotype caused by different mutations. Although other series have suggested that modifier genes may influence the phenotype of *RPGR* mutations, the strong correlation of acuity and field with age would suggest that genetic and environmental factors have little effect on these parameters in this series, supporting the notion that RP due to mutations in *RPGR* is a monogenic disorder.[8]

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