ELECTRONIC LETTER

Mapping a new genetic locus for X linked retinitis pigmentosa to Xq28

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We have defined a new genetic locus for an X linked form of retinitis pigmentosa (RP) on chromosome Xq28. We examined 15 members of a family in which RP appeared to be transmitted in an X linked manner. Ocular examinations were performed, and fundus photographs and electroretinograms were obtained for selected patients. Blood samples were obtained from all patients and an additional seven family members who were not given examinations. Visual acuity in four affected individuals ranged from 20/40 to 20/80+. Patients described the onset of night blindness and colour vision defects in the second decade of life, with the earliest at 13 years of age. Examined affected individuals had constricted visual fields and retinal findings compatible with RP. Based on full field electroretinography, cone function was more severely reduced than rod function. Female carriers had no ocular signs or symptoms and slightly reduced cone electroretinographic responses. Affected and non-affected family members were genotyped for 20 polymorphic markers on the X-chromosome spaced at 10 cM intervals. Genotyping data were analysed using GeneMapper software. Genotyping and linkage analyses identified significant linkage to markers DXS8061, DXS1073, and DXS1108 with two point LOD scores of 2.06, 2.17, and 2.20, respectively. Haplotype analysis revealed segregation of the disease phenotype with markers at Xq28.

Retinitis pigmentosa (RP) is genetically and phenotypically heterogeneous. Patients have progressive night blindness and peripheral visual loss. Loss of central vision occurs late in the course of the disease. All modes of inheritance have been described, with allelic and non-allelic heterogeneity within each genetic category of RP.

X linked RP (XLRP) is generally believed to be the most severe form of RP and has its onset in the first decade of life. Early symptoms include night blindness, visual field defects, and decreased visual function.¹ Significant visual loss is evident usually by the fourth decade. Heterozygous carrier females demonstrate varying degrees of retinal involvement.²⁻³ XLRP accounts for 10–15% of cases of RP.⁴

Five genetic loci have been mapped for XLRP: RP2,⁵ RP3,⁶ RP6,⁷ RP23,⁸ and RP24.⁹ RP2 and RP3 are the most prevalent forms, accounting for 10–20% and 70–90% of XLRP, respectively.^{11–14} The RP2 and RP3 (retinitis pigmentosa GTPase regulator; *RPGR*) genes have been cloned.^{15–19} While initial reports found only 11–26% *RPGR* mutations in families mapping to the RP3 locus,²⁰⁻²¹ the discovery of a novel exon named RPGR-ORF15 allowed the identification of an additional 60% of mutations in patients with XLRP.²² Mutations

in *RP2* and *RPGR* (including ORF15) are believed to account for 50–60% of North American patients with XLRP.²³

Here, we describe a three generation family with X linked RP. Genotyping and linkage analyses with markers covering the entire X chromosome identified a new genetic locus for RP in this family.

MATERIALS AND METHODS

Subjects

Informed consent was obtained from all patients in this study, which was approved by the institutional review board on human subjects of Cleveland Clinic Foundation.

Ocular examinations were conducted on 15 members of this family, including four patients affected with the retinal dystrophy. The oldest affected patient (I-3) could not be brought to the eye clinic for formal examination because of age and difficulty with transportation but he did contribute a blood sample. Examinations included Snellen visual acuity testing, slit lamp biomicroscopy, applanation tonometry, and examination of the lens and fundus after pupillary dilation. Colour vision was tested in all patients using Ishihara plates. Two patients also underwent Farnsworth-Munsell 100 hue testing. Electroretinography (ERG), Goldmann visual field, and dark adaptometry were performed in selected cases as deemed clinically useful. Fundus photography was obtained on selected affected individuals.

Linkage and statistical analysis

In total, 22 blood samples were obtained from affected family members and their parents, children, siblings, and spouses. Genomic DNA was isolated from peripheral blood leucocytes using standard methods.

Genotyping was performed using polymorphic microsatellite markers on the X chromosome from (ABI Prism linkage mapping set MD10; Applied Biosystems Inc., Foster City, CA, USA). In total, 20 markers were chosen at 10 cM intervals throughout the X chromosome. PCR was performed (ABI PCR 9700 system) using standard conditions as described elsewhere.²⁴ After the PCR process, 100 µl of water was added into each reaction well of PCR product and 2 µl was drawn out into a new well. Next, a mix of 12 µl formamide and 0.5 µl ROX size standard was added to each well. The samples were then analysed on an ABI 3100 genetic analyser (Applied Biosystems).

Results were analysed with GeneMapper software (version 1.1). Pairwise LOD scores were calculated with Linkage Package (version 5.2).

Abbreviations: ERG, electroretinography; MAGUK, membrane associated guanylate kinase homologue; RP, retinitis pigmentosa; *RPGR*, retinitis pigmentosa GTPase regulator; XLRP, X linked retinitis pigmentosa

Figure 1 (A) Pedigree of four generation family with XLRP. The affected male and female members are shown by filled squares and circles, respectively. Normal members are shown by open symbols. The deceased individuals are shown by slashes. The proband is shown by an arrow. Note that proband III-6 is a recombinant for three markers: DXS1214, DXS1068, DXS993 and DXS993. (B) Haplotype analysis shows perfect segregation of XLRP with markers DXS8061, DXS1073, and DXS1108. (C) Ideogram of chromosome X with localisation of new RP locus at Xq28. The genetic map with our significant markers and candidate genes we screened is shown.

Mutation screening

Mutation screening of the candidate genes in the linkage interval was carried out using direct DNA sequence analysis. DNA samples from the proband and his normal brother were used. Sequence primers were designed in all coding exons and exon-intron boundaries in two candidate genes. The PCR products were extracted using a commercial kit (QiaQuick gel extraction kit; Qiagen Inc., Valencia, CA, USA), and sequenced with both forward and reverse primers. DNA sequencing analysis was performed using a sequencing kit and genetic analyser (BigDye Terminator cycle sequencing kit, version 1.1, and ABI 3100 analyser; both Applied Biosystems).

RESULTS

Clinical findings

The pedigree structure of the family under study is shown (fig 1), and the clinical features of affected family members are summarised in table 1. Visual acuity in the four examined members ranged from 20/40 to 20/80+. All four described the onset of night blindness and some described colour vision difficulties in the second decade of life, with the earliest at 13 years of age. One had severe abnormalities on the Farnsworth-Munsell 100 hue test, while another had a perfect score. Indirect ophthalmoscopy revealed peripheral bone spicules, waxy pallor of the optic nerve, and attenuated retinal blood vessels (fig 2A) in all patients. All had evidence

Figure 2 (A) Top left shows right inferonasal midperipheral fundus of proband, with some fine pigmentary changes and bony spicules. Top right is a fundus photograph showing waxy pallor and attenuated vasculature in the proband. Bottom panels show progression of visual field defects in the proband's left eye between 1986 (bottom left) and 2002 (bottom right). (B) ERGs recorded from a normal control subject (left), patients III-7 and III-9 (middle), and an asymptomatic carrier, II-7 (right) under standard conditions. The different rows indicate different stimulus conditions: first row, dark-adapted ERG recorded to $-2.0 \log \text{cd s/m}^2$ stimulus; second, dark adapted ERG recorded to $0.5 \log \text{cd s/m}^2$ stimulus; third, light adapted ERG recorded to $0.5 \log \text{cd s/m}^2$ stimulus; fourth, 31 Hz flicker ERG recorded to $0.5 \log \text{cd s/m}^2$ stimulus. Vertical bars indicate time of flash presentation. For both patients and carrier, the responses recorded from the two eyes were averaged together. Note the presence of an A-wave in patients III-7 and III-9 under scotopic conditions, indicating residual rod function. There is no discernible cone function in either patient. Dark adapted recordings obtained from their mother (II-7) were within normal limits, while light adapted responses were reduced in amplitude.

of constricted peripheral vision by Goldman visual field testing (fig 2A). ERG recordings were obtained from two affected family members (III-7 and III-9) and an unaffected obligate carrier (II-7). As shown in fig 2B, dark adapted responses were reduced in amplitude in patients III-7 and III-9, but fell within the range of normal for the obligate carrier. In both III-7 and III-9, light adapted responses, reflecting activity of the cone pathway, were markedly reduced in amplitude. In carrier II-7, light adapted responses retained a normal waveform, but were slightly reduced in amplitude. Thus, in all family members examined, cone ERGs were more severely reduced than were rod responses.

The proband (III-6) first noted the onset of symptoms at 13 years of age. He was formally examined and diagnosed with RP at 16 years, at which time he had 20/20 central vision but already demonstrated peripheral visual field constriction. ERG testing at that time revealed recordable but significantly reduced scotopic and photopic responses (not shown). By 32 years his corrected central visual acuity had decreased to 20/60+ and he had severe constriction of his peripheral vision (fig 2).

Identification of a new genetic locus for RP on Xq28

Genotyping was carried out with 20 markers providing coverage of the entire X chromosome at intervals of 10 cM or less. Analysis of the pairwise LOD scores identified significant linkage to three markers (DXS8061, DXS1073, and DXS1108) on chromosome Xq28 (table 2).

Markers DXS1214, DXS1068, and DXS993 showed positive LOD scores of 0.97, 1.31, and 0.70, respectively (table 1). However, an obligate recombination was observed between each of the three markers with the disease locus in this family as proband III-6 is affected, but carries the normal haplotype for each marker (fig 1A), excluding linkage of the region spanned by these three markers to RP2 and RP3 in this family.

Peak LOD scores of 2.06, 2.17, and 2.20 were obtained for markers DXS8061, DXS1073, and DXS1108 at a recombination fraction of 0.001. In this family, allele 2 of DXS8061, allele 1 of marker DXS1073, and allele 4 of marker DXS1108 co-segregated with the disease (fig 1B). Because a $\text{LOD} \geq 2.0$ indicates significant linkage for X linked disease, our results suggest that a novel RP locus is linked to DXS8061, DXS1073,

Table 1 Clinical features in four patients with X linked RP				
	III-6	III-10	III-7	III-9
Age at collection of blood sample	26	32	32	37
Age at onset of symptoms	13	13	16	16
Best corrected visual acuity at date of sample collection	20/60+ OU	20/40 OU	20/50 OU	20/80+ OD 20/50 OS
Constricted visual fields	Yes	Yes	Yes	Yes
Colour vision deficit	Yes	Not done	No	Yes
ERG	Significantly reduced photopic and scotopic amplitudes	Not done	Significantly reduced photopic and scotopic amplitudes	Significantly reduced photopic and scotopic amplitudes

Table 2 Pairwise LOD scores for markers spaced on chromosome X at 10 cM intervals, assuming an autosomal recessive inheritance pattern

Marker	Maximum recombination fraction	Maximum LOD score	Maximum Recombination fraction (θ)						
			0.00	0.01	0.05	0.10	0.20	0.30	0.40
DXS1060			−∞	−3.93	−1.92	−1.12	−0.42	−0.12	0.0
DXS8051			−∞	−3.83	−1.82	−1.02	−0.34	−0.06	0.03
DXS987			−∞	−4.70	−2.65	−1.81	−1.00	−0.55	−0.23
DXS1226			−∞	−2.12	−0.82	−0.34	0.01	0.11	0.10
DXS1214	0.00	0.97	0.97	0.96	0.88	0.79	0.61	0.42	0.22
DXS1068	0.00	1.31	1.31	1.28	1.18	1.06	0.81	0.55	0.29
DXS993	0.00	0.71	0.71	0.69	0.62	0.55	0.40	0.26	0.13
DXS991			−∞	−1.20	−0.40	0.05	0.20	0.25	0.17
DXS986			−∞	−3.43	−2.03	−1.42	−0.80	−0.44	−0.19
DXS990			−∞	−1.04	−0.36	−0.09	0.12	0.17	0.12
DXS1106			−∞	−1.08	−0.39	−0.11	0.11	0.16	0.12
DXS8055			−∞	2.03	−0.72	−0.23	0.13	0.21	0.16
DXS1001			−∞	2.26	−0.93	−0.41	0.00	0.14	0.13
DXS1047	0.05	0.33	0.32	0.32	−0.33	0.33	0.30	0.24	0.14
DXS1227			−∞	1.28	−0.55	−0.23	0.03	0.11	0.09
DXS8043			−∞	−0.90	−0.12	0.20	0.41	0.39	0.25
DXS8091	0.001	0.71	0.71	0.69	0.64	0.58	0.45	0.31	0.16
DXS8061	0.001	2.06	2.06	2.03	1.90	1.73	1.37	0.97	0.52
DXS1073	0.001	2.17	2.17	2.13	2.01	1.84	1.48	1.06	0.57
DXS1108	0.001	2.20	2.20	2.17	2.04	1.88	1.51	1.08	0.59

LOD scores were computed with the assumption of a disease gene frequency of 0.00001, 99.999% penetrance, and 0.00001 phenocopy.

and DXS1108 on Xq28. Markers DXS1047, DXS1227, DXS8043 and DXS8091 that span the RP24 locus showed recombination in IV-6, excluding the RP24 gene as the gene in this family.

RPGR and the *RP2* genes had been previously screened in one of the affected members and no mutation was found (A Swaroop, personal communication).

Mutation screening results

Two candidate genes that lie between DXS8061 and DXS1108 were screened: *CNGA2* (encoding the $\alpha 2$ subunit of the cyclic nucleotide gated channel) and *MPP1* (encoding membrane protein, palmitoylated 1) (fig 1C). We sequenced all coding exons and exon-intron boundaries, but no disease causing mutation was identified in either gene.

DISCUSSION

The clinical phenotype of this family is characterised by onset of symptoms in the second decade of life and a progressive loss of peripheral vision in the ensuing decades. Central acuity is maintained to better than 20/80 into the sixth decade. The appearance of the fundus is compatible with RP with distinct peripheral pigmentary changes, optic pallor, and attenuated retinal vessels; no macular atrophic changes were present. Nevertheless, ERG responses were preserved into the fourth decade of life and were remarkable for a more severe involvement of cones than rods. A similar pattern of more significant cone involvement had led to the labelling of some families with RPGR ORF15 mutations as having cone dystrophy.²⁵ We cannot rule out that the present family has an unusual type of cone-rod dystrophy; however the predominant symptom of night blindness, peripheral field defects, and absence of light sensitivity, photophobia and macular atrophic changes, suggest that this is a form of RP rather than a cone dystrophy such as COD2, the gene locus of which may overlap with the locus that we defined here.²⁶ Patients with COD2 have a number of clinical features that distinguish them from the patients studied here. In particular, patients with COD2 have early onset photophobia, colour vision defects, and macular atrophic changes.²⁷ Patients with COD2 also have a normal scotopic ERG and the fundus does not show peripheral pigmentary changes.²⁷

Genotyping of family members using markers spanning the entire X chromosome allowed the identification of a new locus linked to DXS8061, DXS1073, and DXS1108. This new RP locus on Xq28 is distinct from RP24, which is located in an interval between DXS1047 and DXS8043. The entire RP24 locus showed recombination with proband III-6 in the family (fig 1B). Furthermore, three markers linked to the new RP locus (DXS8061, DXS1073, and DXS1108) are all located outside the RP24 locus.

This new RP locus contains more than 100 known and putative genes. Of the genes in the disease interval, we selected two genes for mutation analysis. *CNGA2* mediates sensory transduction in olfactory neurones and retinal photoreceptor cells.²⁸ All six coding exons and exon-intron boundaries were sequenced, but no mutation was identified. *MPP1* is the prototype of a family of membrane associated proteins termed membrane associated guanylate kinase homologues (MAGUKs),²⁹ which interact with the cytoskeleton and regulate cell proliferation, signalling pathways, and intracellular junctions. *MPP4*, another MAGUK, has been implicated in RP.³⁰ No mutation was found in *MPP1*. Further studies focusing on other candidate genes at this new RP locus may identify a novel molecular determinant for the pathogenesis of RP.

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