A new genetic locus for X linked progressive cone-rod dystrophy

R Jalkanen, F Y Demirici, H Tyynismaa, T Bech-Hansen, A Meindl, M Peippo, M Mäntyjärvi, M B Gorin, T Alitalo

X linked progressive cone-rod dystrophy (COD) is a retinal disease primarily affecting the cone photoreceptors. The disease is genetically heterogeneous and two loci, COD1 (Xp21.1-11.4) and COD2 (Xq27.2-28), have been previously identified. COD1 was recently shown to be caused by mutations in RPGR exon ORF15 (Xp2.1.1), the gene that is also responsible for RP3 type retinitis pigmentosa. In this study, we performed a linkage study to map the disease gene in a large Finnish family with X linked cone-rod dystrophy, using a panel of 39 X chromosomal markers. Several recombinations between the disease gene and markers in the Xp21.1-p11.4 region have excluded COD1 as a candidate locus in this family. Consistent with the linkage results, no mutation was detected by direct PCR sequencing of the coding region of RPGR, including exon ORF15. The COD2 locus has also been excluded as the site of the gene on the basis of negative lod score values obtained for COD2 linked markers. The disease causing gene of the studied COD family has been localised between the markers DXS10042 and DXS8060 on Xp11.4-q13.1. Positive pairwise lod scores >3 were obtained for markers DXS993, MAOB, DXS1055, and DXS1194. Since this locus is distinct from the previously identified two loci, COD1 and COD2, our results establish a new third genetic locus for X linked progressive cone-rod dystrophy and further expands our knowledge about the genetic heterogeneity underlying this disease entity.

ORIGINAL ARTICLES


X linked recessive cone-rod dystrophy (COD) is a progressive visual disorder primarily affecting the cone cells of the retina. Affected males show reduced visual acuity, moderate or high myopia, photophobia, defects in colour vision, central scotomas, and affected cone or cone-rod responses in the electroretinogram (ERG).1,2 Variable changes in the fundus have been reported ranging from dark granular macula to geographical atrophy of the retinal pigment epithelium3,4 and tapetal-like sheen of the retina.5,6 The disease usually begins in childhood and progresses gradually; however, some patients may develop the disease later in adulthood and in such cases the progression has been reported to be slower.7 The phenotypic expression of the disease is variable, and may even vary among sibs, with respect to age at onset and severity of symptoms and findings.8 Female carriers may be clinically normal or present variable symptoms, including mild impairment of visual acuity, light sensitivity, and slight abnormalities in colour vision and ERG.9

X linked progressive cone-rod dystrophy is a genetically heterogeneous disorder and two distinct loci (COD1 and COD2) have been previously identified. A number of linkage studies were performed to determine the location of COD1 on Xp21.1-11.410–14 and our collaborative efforts recently identified RPGR (exon ORF15) as the disease causing gene in the original COD1 families.15 These latest results were also supported by another independent study.11 Despite the former description of COD1 as a cone dystrophy,1 the subsequent evaluation of additional patients from this original family and other families showed a quite variable extent of cone and rod involvement among affected males.16,17 Though all of the affected subjects showed some of the features associated with primary cone abnormalities, most also showed rod dysfunction and significant rod involvement was also observed in some patients.18 Therefore, we prefer using “X linked cone-rod dystrophy” instead of “X linked cone dystrophy”, in order to ensure that readers will not think that the rods are spared during the course of the disease, although the COD abbreviation is still maintained as it was originally used for locus assignment. RPGR was first identified in 1996 as the causative gene for RP3 type retinitis pigmentosa.12 The subsequent discovery of exon ORF15 (a new alternative 3′ exons of RPGR) by Vervoort et al13 disclosed a mutational hotspot, which is consistent with the highly repetitive nature of this new exon. Several different exon ORF15 mutations have been identified in RP3 families to date14,15 and RP15 was also shown to be caused by a mutation in RPGR exon ORF15.16 Recent findings indicate that COD1 is also allelic to RP3, and RPGR mutations may encompass a broad spectrum of retinal diseases, also including an X linked recessive atrophic macular degeneration phenotype.17

In addition to COD1, a second locus (COD2) has been described by Bergen and Pinckers,18 who performed linkage studies in an X linked progressive cone dystrophy family and mapped the disease locus between markers DXS292 and DXS1113 on Xq27. Based on the current genetic and physical map of NCBI (http://www.ncbi.nlm.nih.gov/), the COD2 locus is localised to Xq27.2-q28. Two other studies of cone dystrophy have been published in which the patients had deletions either in the red cone pigment gene19 or near the 5′ end of the red cone pigment gene20 on Xq28. There are no data available on whether the red and green pigment genes, RCP and GCP, have been sequenced and excluded in COD2 patients.21

Here we present the linkage and candidate gene screening results in a large Finnish family with X linked progressive cone-rod dystrophy. We have determined the genetic interval of a new COD locus and screened nine candidate genes within the linked region for mutations.

MATERIALS AND METHODS

Subjects
Members of the X linked cone-rod dystrophy family who gave a blood sample and participated in the genetic study are
shown in fig 1. Clinical studies of the family members have been published elsewhere, including a complete pedigree of the family. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in accordance with the requirements of the University of Kuopio Ethics Committee. DNA was extracted from the collected blood samples using a non-enzymatic method.

**DNA markers and linkage analysis**

A total of 50 family members, including seven affected males, were genotyped using 37 microsatellite markers from the Xp22.32-q28 region and two intragenic SNPs from the RPGR gene. Primer sequences for most of the microsatellite markers were obtained from the Genome Database (http://www.gdb.org). The following two primer pairs were used to obtain the PCR amplified genomic fragments that currently harbour four intronic SNPs (rs3896245, rs3888228, rs3891252, and rs3015258) from the NCBI SNP database: rs1111401F, 5′-GCATGTCCATTTGAGTACAAAG-3′; rs1111401R, 5′-CATGTCTTTGCTTGGTGTTG-3′; rs1075939/rs1079728F, 5′-CCAGGTTCAAGCGATTCTC-3′; rs1075939/rs1079728R, 5′-ATGAAGGCCCTGAAATTACC-3′. The genomic fragment, which was amplified with rs1111401-primers, is located in intron 17 and contains the SNP rs3896245. The fragment amplified with rs1075939/rs1079728 primers lies in intron 18 and contains SNPs rs3888228, rs3891252, and rs3015258. The SNP rs3888228 was used in the linkage analysis, as well as the previously undescribed SNP A/T (named here SNP1) which is located in the same PCR fragment as rs3896245, 101 bp upstream from it. Allele frequencies for SNP1 are 0.27 for A and 0.73 for T. PCR conditions were as follows: 94°C for 10 minutes, followed by 35 cycles of 94°C for one minute, 56°C for one minute, and 72°C for one minute, followed by a final extension at 72°C for 10 minutes. SNPs were evaluated using single strand conformational analysis (SSCA) and gels were visualised by silver staining. Two new microsatellite markers (CA repeats) were identified from the Genbank sequence (accession number AC006121). Primers for these markers are: CA20F, 5′-GAAGGTAAGTTGTGATGTGAGCTG-3′; CA20R, 5′-AAACAACTCTCTTGGCTTTACTCC-3′; CA23F, 5′-GAACAGCAAACCAATCCAAA-3′; CA23R, 5′-GGCCTATGGTAATGCTCCCTCT-3′. Markers CA20 and CA23 are located 165 kb and 212 kb distal to DXS993, respectively. Expected heterozygosity, which was calculated using allele frequencies of 50 normal male controls, was 92% for CA23 and 92.7% for CA20. Markers were amplified by PCR and the products were separated on 6% polyacrylamide gels. PCR conditions were similar to those described above, except that the annealing temperature was 59°C and the number of extension cycles was 32. Two point linkage analysis was performed using the MLINK option of the FastLink package, version 4.1P. X linked inheritance with full penetrance and a disease allele frequency of 0.00001 were assumed. Allele frequencies for microsatellite markers were obtained from the healthy members of the Finnish COD family.

**Mutation analysis**

An affected family member and an obligate carrier female were included in the mutation analysis. A total of nine genes, mapping to the Xp21.1-Xq12 region, were analysed, including
ABI PRISM the QIAquick PCR Purification kit (Qiagen GmbH, Hilden,) sequencing all the exons. PCR fragments were purified with

cone-rod dystrophy was in childhood and in two patients
In eight of our patients the onset of X linked progressive
Clinical studies

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**Table 1** Pairwise lod score values between the disease gene and X chromosomal markers. The genetic locations of the markers were obtained from the Marshfield Comprehensive human genetic map and physical locations from the STS map of the National Center for Biotechnology Information (NCBI). Undetermined locations are indicated by –.

**Linkage data**

Linkage analysis was performed using 39 markers covering both the COD1 and COD2 regions (Xp22.32-q28). Results of the two point linkage analysis are summarised in table 1. Close linkage with no recombinations was observed between cone-rod dystrophy and markers CA23, CA20, DXS993 (Zmax=3.90 at θ=0.00), DXS8012, DXS1201, MACB (Zmax=3.48 at θ=0.00), DXS1055 (Zmax=3.18 at θ=0.00), DXS1194 (Zmax=4.10 at θ=0.00), DXS1275, and DXS559. The closest flanking markers, which showed recombinations with respect to the disease locus, were DXS10042 on the distal side and DXS8060 on the proximal side. The distance between these markers is approximately 35 cM (estimated from the Marshfield Comprehensive human genetic map in url: http://research.marshfieldclinic.org/genetics/). Recombinations clearly in adulthood. All of them showed decreased visual acuities, moderate to high myopia, red or red-green colour vision defects, central scotomas (in some patients also concentric constriction in visual fields), affected cone and rod thresholds in dark adaptation, and diminished cone or cone-rod responses by full field ERG. The eye fundi showed irregular pigmentation or myopic changes in the macular area. The 12-14 year follow up study of four patients did not show significant progression of the disease. The six obligate carriers who were examined had normal vision.

**RESULTS**

**Clinical studies**

The results of thorough clinical examinations have been published elsewhere. The complete family pedigree included 10 affected males, of whom seven participated in genetic studies. In eight of our patients the onset of X linked progressive cone-rod dystrophy was in childhood and in two patients

RPGR (MIM 312610), DXD3 (MIM 300160), NYX (MIM 300278), GPR3 (MIM 300241), I-4, NDP (MIM 310600), RP2 (MIM 312600), TIMP1 (MIM 305370), and ARR3 (MIM 301770). Exons and exon-intron junctions were amplified by PCR and screened for mutations. The promoter region of the NDP gene (945 bp) was also included in the screening. Primer sequences and PCR conditions are available on request. Mutation analysis was performed by SSCP as described previously. In addition to SSCP, eight of the genes were also fully sequenced (from one patient) using an ABI PRISM® 310 Genetic Analyzer. The RPGR gene was screened only by sequencing the exons. PCR fragments were purified with the QIAGEN PCR Purification kit (Qiagen GmbH, Hilden, Germany). Sequencing reactions were performed using the ABI PRISM® BigDye® Terminator v3.0 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and purified with Edge Gel Filtration Cartridges (EdgeBioSystems, Gaithersburg, MD).
were observed in one patient and one obligate carrier (distal region) and in two patients and one obligate carrier (proximal region, fig 1).

Negative lod score values were obtained with all markers of the COD2 region, thus excluding the Xq27-q28 region (table 1). Recombinations (in one affected and one unaffected subject) were also found between the disease gene and markers of the COD1 locus, including an intragenic SNP, SNP1, of the RPGR gene, also excluding the COD1 locus as the site of the causative gene in the Finnish cone-rod dystrophy family (table 1).

Based on the information obtained from church registers, it was previously concluded that the disease segregating in the Finnish family was most likely inherited from the female I.2. However, in this study we could observe two distinct non-recombinant haplotypes (and one recombinant haplotype), in addition to the disease haplotype, in obligate carriers of the second generation, indicating that the disease haplotype was inherited from the father I.1 (fig 1).

**Mutation screening results**

A total of nine candidate genes from the Xp21.1-Xq12 region was included in the mutation analysis: the disease genes for COD1 and retinitis pigmentosa 3 (RPGR), retinitis pigmentosa 2 (RP2), congenital stationary night blindness (NYX), Norrie disease (NDP), and five other genes, DDX3, GPR34, I-4, TIMP1, and ARR3 (fig 2). No disease causing mutations were identified in any of these genes. All the identified sequence alterations were located in intronic or untranslated regions and were also observed in 50 normal male control samples, indicating that the changes were polymorphisms instead of disease causing mutations (data not shown). The coding region (exons and flanking exon-intron junctions) of RPGR, including exon ORF15, was also sequenced in the DNA from one of the affected family members but no alterations were found.

**DISCUSSION**

In this study we have identified a new and third locus for X linked progressive cone-rod dystrophy. Linkage data suggest that the gene is localised to the centromeric region of the X chromosome, between markers DXS10042 and DXS8060. The critical interval corresponds to a 35 cm region localised to Xp11.4-Xq13.1. The data clearly exclude the COD1 and COD2 loci as sites of the causative gene for cone-rod dystrophy in the family evaluated in this study. In addition to RPGR, eight candidate genes were screened but no mutations were identified.

The primary symptoms of our patients were decreased visual acuity, moderate to high myopia, and red or red-green colour vision defects. In addition, the onset of the disease was usually in childhood and the progression of the disease was slow: Table 2 summarises the clinical characteristics of the X linked recessive COD families for which the genetic locus has been assigned. Meire et al reported similar symptoms and similar fundus and ERG findings in six related male patients with X linked cone-rod dystrophy. In dark adaptation, the cone-rod thresholds were missing and also in one of their patients rod threshold was slightly raised as in our patients. However, in the oldest patient of Meire et al (86 years), colour vision defect had progressed to acquired achromatopsia, while our oldest patient (81 years) had only red-green defect. The visual field defects were also different; the patients of Meire et al had central scotomas while some of our patients had both central and peripheral defects. Their candidate gene region (Xp21.1-p11.3) overlaps partly with ours, but because it also encompasses the RP3 region, it is still possible that their patients have a mutation in the RPGR gene. Our family also shows similarities to the COD1 families with known RPGR mutations, with respect to disease onset and progression and association with myopia.

The clinical features of COD2 (Xq27.2-q28) are also very similar to those of COD1, although the early stages in COD2 family members were characterised by peripheral cone
degeneration in contrast to the central cone disease observed in COD1 families. However, clinically it is still difficult to distinguish these two entities. In addition to COD1 and COD2, two studies described progressive cone dystrophy phenotypes associated with deletions either in the red cone pigment gene or near the 5’ end of the red cone pigment gene on Xq28. These patients also showed decreased visual acuity, reduced cone responses in ERG, and colour vision defects, although no progression to cone-rod dystrophy was observed. Both of these cone dysfunctions are congenital and show no progression to cone-rod dystrophy, and colour vision defects, Xq28. These patients also showed decreased visual acuity, decreased cone responses in ERG, and colour vision defects.

Table 2: The genetic and clinical features of X linked recessive COD loci

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References: Barlent et al., Jacobson et al., Hong et al., Seymour et al., Brown et al., Bergen et al., Meire et al., Mantyjarvi et al., this study, Pinckers and Timmerman, Bergen and Pinckers.

General ophthalmological characteristics:
- Onset within the first three decades and usually before the age of 20.
- Gradual progression of visual loss, photophobia, moderate to high myopia.
- Very slow progression of visual loss, high myopia.
- Slight progression of visual loss, moderate to high myopia.

Visual fields:
- Generalised depression in younger patients, central scotomas in older patients, peripheral dysfunction in few cases.
- Central scotomas.
- Central sensitivity reduction, central scotomas, concentric constriction.
- Central sensitivity decrease, central scotomas.

Colour vision:
- Mixed deutan-tritan defect, type I red-green defect, errors with no specific axis, no colour perception in advanced cases.
- Red-green defects, no colour perception in advanced cases.
- Red or type I red-green defects.
- Type I red-green defect, primarily red cones are affected, no colour perception in advanced cases.

Electroretinogram (ERG):
- Severe cone dysfunction early in life, moderately reduced rod responses in all age groups.
- Severe cone dysfunction, reduced rod responses in later stages.
- Defective cone responses in all, diminished rod responses in some cases.
- Reduced cone ERG, reduced rod ERG in later stages.

Fundus:
- Ranges from granular macula in younger patients to bull’s eye and geographical atrophy of the RPE in older patients ± tapetal-like sheen, thin peripheral RPE, peripapillary atrophy.
- Ranges from granular macula in younger patients to geographical atrophy in older patients, no tapetal reflex, myopic degeneration with prominent choroidal pattern.
- Only myopic changes and irregular pigmentation in the macular area, no tapetal reflex, no bull’s eye appearance.
- Little pigment clumping, no tapetal reflex, myopic degeneration, chorio-capillary atrophy.

Molecular defect:
- Mutations in RPGR exon ORF15 (Demirci et al., Yang et al.)
- Not described yet.
- Not described yet.
- Not described yet.

Allergic diseases, that is, different phenotypes that are the result of different mutations in a single gene, are not rare among retinal diseases. Another example, in addition to COD1 and RP3, is the spectrum of phenotypes associated with mutations in ABCA4 (MIM 601691). Mutations in ABCA4 can give rise to autosomal recessive retinitis pigmentosa, cone-rod dystrophy, Stargardt disease, and fundus flavimaculatus. The disease interval on Xp11.4-q13.1 reported here contains many known genes that are either expressed in the retina or are already known to cause retinal diseases. The genes for retinitis pigmentosa 2 (RP2, MIM 312600), the complete form of congenital stationary night blindness, CSNB1 (NXY, MIM 300278) and Norrie disease (NDP, MIM 310600) were considered as potential candidates for our family. However, sequencing of the coding regions did not show any disease causing mutations. Because only a single family has been investigated, there remains the possibility of a novel mutation in one of the
genes outside the coding regions that could affect the splicing or stability of the RNA transcript. A number of other retinal diseases map to the candidate gene region; these include the incomplete form of congenital stationary night blindness (CSNB2, MIM 300071) caused by mutations in the CACNA1F gene (MIM 300110), Åland Island eye disease (AIED, MIM 300600), X-linked optic atrophy (OPA2, MIM 311050), and primary retinal dysplasia (PRD, MIM 312550). The screening of additional candidate genes within the critical region is in progress in our laboratory. Although the gene responsible for this disease in this Finnish family remains to be identified, closely linked markers introduced in this study can already be used in carrier diagnosis. The characterisation of the gene in this new locus will expand our knowledge and further our understanding of the biology pertaining to cone-rod dystrophies.

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A new genetic locus for X linked progressive cone-rod dystrophy

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