

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

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

*J Med Genet* 2003;40:418–423

See end of article for authors' affiliations

Correspondence to:  
Dr T Alitalo, Helsinki  
University Central Hospital,  
Department of OB/GYN,  
Genetics, Haartmaninkatu  
2, PO Box 140, Helsinki,  
00029 HUS, Finland;  
Tiina.Alitalo@hus.fi

Revised version received 6  
March 2003  
Accepted for publication 6  
March 2003

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 (Xp21.1), 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 been also 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.

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).<sup>1,2</sup> Variable changes in the fundus have been reported ranging from dark granular macula to geographical atrophy of the retinal pigment epithelium<sup>3,4</sup> and tapetal-like sheen of the retina.<sup>4,5</sup> 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.<sup>2</sup> 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.<sup>6</sup> 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.<sup>1</sup>

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 Xp21.1-11.4<sup>7–10</sup> and our collaborative efforts recently identified *RPGR* (exon ORF15) as the disease causing gene in the original *COD1* families.<sup>10</sup> These latest results were also supported by another independent study.<sup>11</sup> Despite the former description of *COD1* as a cone dystrophy,<sup>1</sup> 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.<sup>4,6</sup> 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.<sup>4,6</sup> 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.<sup>12</sup> The subsequent discovery of exon ORF15 (a new alternative 3' exon of *RPGR*) by Vervoort *et al*<sup>13</sup> 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 date<sup>14,15</sup> and RP15 was also shown to be caused by a mutation in *RPGR* exon ORF15.<sup>16</sup> 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.<sup>17</sup>

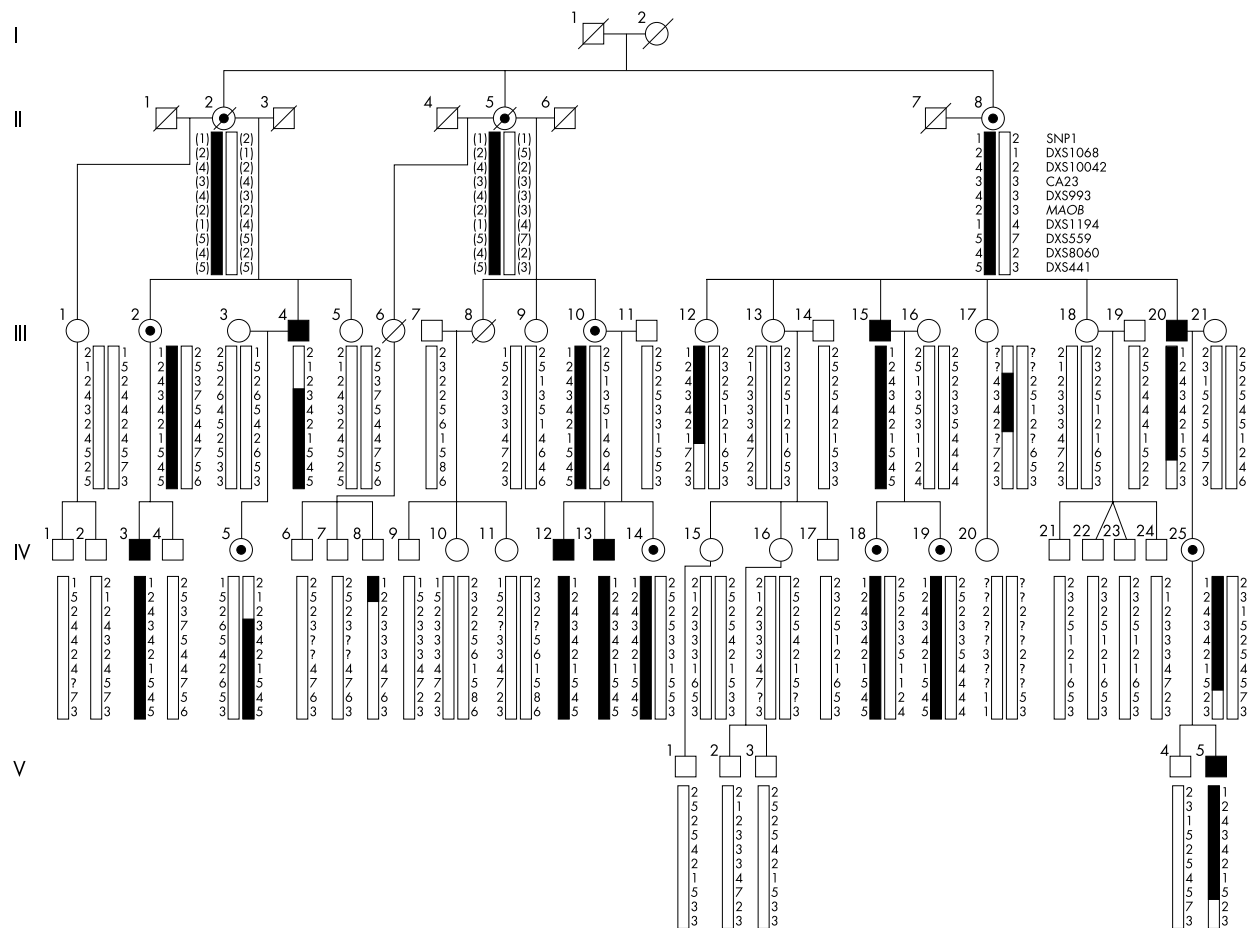
In addition to *COD1*, a second locus (*COD2*) has been described by Bergen and Pinckers,<sup>18</sup> who performed linkage studies in an X linked progressive cone dystrophy family and mapped the disease locus between markers DXS292 and DXS1113 on Xq27. Based on the current genetic and physical map 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 gene<sup>19</sup> or near the 5' end of the red cone pigment gene<sup>20</sup> 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.<sup>18</sup>

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



**Figure 1** Partial pedigree of the Finnish COD family depicting only those family members who participated in the genetic study. Haplotypes are shown below each person; black bars indicate the disease haplotype. The alleles in parentheses indicate that the alleles were drawn from the offspring. The potential carrier status of III.12 and III.17 could not be defined because of the lack of sons and grandsons.

shown in fig 1. Clinical studies of the family members have been published elsewhere, including a complete pedigree of the family.<sup>2</sup> 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.<sup>21</sup>

#### 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'-CATGTCTTTGCTTGGTGTG-3'; rs1075939/rs1079728F, 5'-CCAGGTCAAGCGATCTC-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.<sup>22</sup> 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'-AAACAACCTCTCTGGCTTTACTCC-3'; CA23F, 5'-GAACAGCAAACCAAATCCAAA-3'; CA23R, 5'-GGCCTATGGTAATGCC TCCT-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 FastLink package, version 4.1P.<sup>23</sup> 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

**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 –

Marker	Mb	cM	Lod score at recombination fraction of						
			0.0	0.1	0.2	0.3	0.4	0.5	
DXS8051	Xp22.32	8.32	12.03	∞	-2.54	-1.27	-0.63	-0.25	0.00
DXS1053	Xp22.31	14.39	22.04	∞	-0.65	0.02	0.18	0.14	0.00
DXS1229	Xp22.13	19.23	32.98	∞	-0.48	-0.22	-0.08	-0.02	0.00
DXS1048	Xp22.11	25.45	37.35	∞	-1.69	-0.57	-0.15	-0.02	0.00
DXS1242	Xp21.2	31.86	–	0.31	0.29	0.24	0.18	0.10	0.00
DXS1110	Xp21.1	35.81	–	∞	0.16	0.29	0.27	0.17	0.00
rs3888228	Xp21.1	36.23	–	0.05	0.05	0.05	0.04	0.02	0.00
SNP1	Xp21.1	36.23	–	∞	0.81	0.80	0.58	0.29	0.00
DXS1068	Xp11.4	37.01	52.63	∞	2.28	1.99	1.47	0.79	0.00
DXS8025	Xp11.4	37.63	52.63	∞	1.42	1.21	0.83	0.36	0.00
DXS556	Xp11.4	37.81	–	∞	2.62	2.22	1.62	0.86	0.00
DXS8015	Xp11.4	37.89	53.71	∞	1.13	1.05	0.78	0.40	0.00
DXS8042	Xp11.4	37.95	53.71	∞	1.12	1.07	0.79	0.39	0.00
DXS10042	Xp11.4	38.87	–	∞	2.53	2.10	1.47	0.72	0.00
CA23	Xp11.4	38.96	–	1.78	1.57	1.27	0.90	0.48	0.00
CA20	Xp11.4	39.01	–	1.89	1.66	1.35	0.97	0.52	0.00
DXS993	Xp11.4	39.17	62.50	3.90	3.22	2.49	1.68	0.78	0.00
DXS8012	Xp11.4	–	62.50	0.92	0.80	0.65	0.47	0.25	0.00
DXS1201	Xp11.4	40.28	63.59	2.26	1.94	1.55	1.11	0.59	0.00
MAOB	Xp11.3	41.64	–	3.48	2.90	2.27	1.57	0.79	0.00
DXS1055	Xp11.23	45.23	72.38	3.18	2.66	2.08	1.45	0.74	0.00
DXS1194	Xq11.2	61.64	83.30	4.10	3.39	2.63	1.78	0.83	0.00
DXS1275	Xq12	64.69	89.91	2.95	2.47	1.96	1.38	0.71	0.00
DXS559	Xq12	67.06	–	2.67	2.18	1.66	1.09	0.48	0.00
DXS8060	Xq13.1	69.27	93.17	∞	1.99	1.66	1.15	0.55	0.00
DXS441	Xq13.1	71.16	–	∞	1.88	1.55	1.07	0.52	0.00
DXS1225	Xq13.2	73.76	93.17	∞	1.23	1.05	0.70	0.30	0.00
DXS6801	Xq21.31	89.49	99.73	∞	0.82	0.88	0.67	0.35	0.00
DXS8096	Xq22.1	99.69	110.72	∞	-0.17	0.25	0.32	0.23	0.00
DXS8059	Xq25	119.16	135.96	∞	-1.17	-0.15	0.19	0.22	0.00
DXS8071	Xq26.2	128.28	144.78	∞	-1.44	-0.37	0.03	0.13	0.00
DXS1227	Xq27.1	137.66	155.88	∞	-1.18	-0.39	-0.10	0.01	0.00
DXS8043	Xq27.3	138.56	167.87	∞	-2.20	-0.98	-0.41	-0.12	0.00
DXS998	Xq27.3	141.13	173.40	∞	0.01	0.45	0.44	0.24	0.00
DXS1215	Xq28	141.79	175.32	∞	-2.41	-0.94	-0.30	-0.03	0.00
DXS1123	Xq28	143.01	–	∞	-1.90	-0.71	-0.19	0.01	0.00
DXS8061	Xq28	146.31	181.08	∞	-1.20	-0.31	0.05	0.13	0.00
DXS9897	Xq28	146.62	–	∞	-2.16	-0.92	-0.33	-0.06	0.00
DXS1073	Xq28	147.89	184.34	∞	-0.50	-0.06	0.10	0.11	0.00

*RPGR* (MIM 312610), *DDX3* (MIM 300160), *NYX* (MIM 300278), *GPR34* (MIM 300241), *I-4*, *NDP* (MIM 310600), *RP2* (MIM 312600), *TIMPI* (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 SSCA as described previously.<sup>24</sup> In addition to SSCA, 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 all the exons. PCR fragments were purified with the QIAquick 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).

## RESULTS

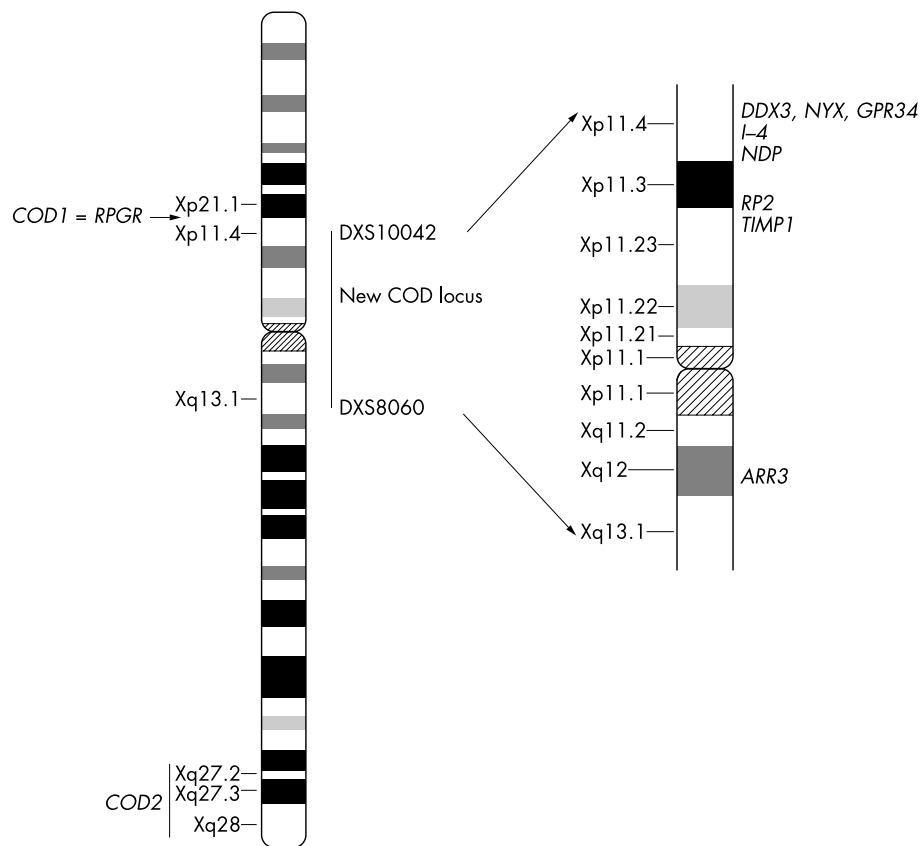
### Clinical studies

The results of thorough clinical examinations have been published elsewhere.<sup>2</sup> 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

clearly in adulthood. All of the patients 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.

### 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 ( $Z_{max}=3.90$  at  $\theta=0.00$ ), DXS8012, DXS1201, *MAOB* ( $Z_{max}=3.48$  at  $\theta=0.00$ ), DXS1055 ( $Z_{max}=3.18$  at  $\theta=0.00$ ), DXS1194 ( $Z_{max}=4.10$  at  $\theta=0.00$ ), 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



**Figure 2** Location of *COD1*, *COD2*, the newly identified COD locus, and the candidate genes analysed.

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.<sup>2</sup> 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,<sup>25</sup> 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*<sup>5</sup> 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*<sup>5</sup> (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*<sup>5</sup> 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

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

	Locus			
	Xp21.1-11.4 ( <i>COD1</i> )	Xp21.1-11.3, may be either <i>COD1</i> (left column) or the newly described locus (right column)	Xp11.4-q13.1 (new locus)	Xq27.2-q28 ( <i>COD2</i> )
References	Bartley <i>et al</i> , <sup>7</sup> Jacobson <i>et al</i> , <sup>1</sup> Hong <i>et al</i> , <sup>6</sup> Seymour <i>et al</i> , <sup>9</sup> Brown <i>et al</i> <sup>8</sup>	Bergen <i>et al</i> , <sup>8</sup> Meire <i>et al</i> <sup>6</sup>	Mäntyjärvi <i>et al</i> , <sup>2</sup> this study	Pinckers and Timmerman, <sup>31</sup> Bergen and Pinckers <sup>18</sup>
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	Gradual progression of visual loss, high myopia	Onset within the first three decades and usually in childhood Very slow progression of visual loss moderate to high myopia	Onset in early childhood 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 young 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, choriocapillary atrophy
	Central cone disease progressing to diffuse cone-rod dysfunction: early colour vision impairment with a severity parallel to the degree of visual acuity impairment	Central cone disease progressing to diffuse cone-rod dysfunction	Central cone disease progressing to diffuse cone-rod dysfunction	Peripheral cone disease progressing to diffuse cone-rod dysfunction: colour vision becomes impaired later compared to visual acuity and ERG
Molecular defect (References)	Mutations in <i>RPGR</i> exon ORF15 (Demirci <i>et al</i> , <sup>10</sup> Yang <i>et al</i> <sup>11</sup> )	Not described yet	Not described yet	Not described yet

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<sup>19</sup> or near the 5' end of the red cone pigment gene<sup>20</sup> 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 either a protan (red) defect in colour vision<sup>19</sup> or incomplete achromatopsia with a little function only in blue cones.<sup>20</sup> No tendency to any particular refractive error could be found, and nystagmus was a common sign in blue cone monochromacy (BCM) patients. The diseases described by Reichel *et al*<sup>19</sup> and Nathans *et al*<sup>20</sup> can thus be distinguished clinically from *COD1* and our patients. The clinical features of Bornholm eye disease (BED) include impaired central vision, myopia, optic nerve pallor, and deuteranopia.<sup>26</sup> Linkage analysis has shown that the locus maps to the distal end of Xq<sup>27</sup> and the mutation responsible for BED could be allelic with the *COD2* locus.

In general, it is difficult to distinguish progressive cone-rod dystrophies clinically, both X linked and autosomal forms, from each other. The clinical symptoms and findings in functional eye examinations, such as visual fields, dark adaptation,

and electroretinogram, are very similar. Therefore, in spite of the present results suggesting a new locus for X linked progressive cone-rod dystrophy, it is not surprising that our patients have similar clinical symptoms and findings in functional tests to the patients with either *COD1* or *COD2*. Of the previously described X linked COD families, the cone-rod dystrophy phenotype described by Meire *et al*<sup>6</sup> most closely matches the clinical picture of our patients.

Allelic 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,<sup>28</sup> cone-rod dystrophy,<sup>28</sup> Stargardt disease,<sup>29</sup> and fundus flavimaculatus.<sup>30</sup> 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* (*NYX*, 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 the 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.

## ACKNOWLEDGEMENTS

We thank the members of the COD family for participation, Sinikka Lindh, Terttu Myöhänen, and Marjatta Sipponen for their help in collecting blood samples, and Johanna Tommiska for technical assistance. This work was supported by a grant (TYH1338) from the Finnish State (TA), by the NIH Grant EY13130 (MBG), by the Eye & Ear Foundation of Pittsburgh, Pittsburgh, PA (MBG), and by Research to Prevent Blindness, NY, NY.

## Authors' affiliations

**R Jalkanen, H Tynnismaa, T Alitalo**, Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland  
**F Y Demirci, M B Gorin**, Departments of Ophthalmology and Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA  
**T Bech-Hansen**, Department of Medical Genetics, University of Calgary, Calgary, Alberta, Canada  
**A Meindl**, Department of Medical Genetics, Ludwig-Maximilians University, Munchen, Germany  
**M Peippo**, Department of Medical Genetics, the Family Federation of Finland, Helsinki, Finland  
**M Mäntyjärvi**, Department of Ophthalmology, University of Kuopio, Kuopio, Finland

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