X linked progressive cone-rod dystrophy (COD) 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 and our collaborative efforts recently identified RPGR (exon ORF15) as the disease causing gene in the original COD1 families. These latest results were also supported by another independent study. Despite the former description of COD1 as a cone dystrophy, 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.

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'-CCAGGTCAAGGGATCTC-3'; rs1075939/rs1079728R, 5'-ATGAGGGCCTGAATTACC-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'-GAAGGTAAGTGATGTGAGCTG-3'; CA20R, 5'-AAACAACTCTCTTGCCCTTACTC-3'; CA23F, 5'-GAACAGCAACCAAAATCCAAA-3'; CA23R, 5'-GGGCTATGGTAAATCGC TCC3'-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 4.1. 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
Germany. Sequencing reactions were performed using the Applied Biosystems (Foster City, CA) and purified with Edge. sequences and PCR conditions are available on request. Muta-

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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 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 (Zmax=3.90 at θ=0.00), DXS8012, DXS1201, MAOB (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

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.
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 \textit{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 \textit{COD1} locus, including an intragenic SNP, SNP1, of the \textit{RPGR} gene, also excluding the \textit{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 obligate carriers of the second generation, indicating that the disease haplotype was inherited from the father I.1 (fig 1).

\textbf{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 \textit{COD1} and retinitis pigmentosa 3 (\textit{RPGR}), retinitis pigmentosa 2 (\textit{RP2}), congenital stationary night blindness (\textit{NYX}), Norrie disease (\textit{NDP}), and five other genes, \textit{DDX3}, \textit{GPR34}, I-4, \textit{TIMP1}, and \textit{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 \textit{RPGR}, including exon ORF15, was also sequenced in the DNA from one of the affected family members but no alterations were found.

\textbf{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 \textit{COD1} and \textit{COD2} loci as sites of the causative gene for cone-rod dystrophy in the family evaluated in this study. In addition to \textit{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\textsuperscript{3} 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\textsuperscript{3} (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\textsuperscript{3} 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 \textit{RP3} region, it is still possible that their patients have a mutation in the \textit{RPGR} gene. Our family also shows similarities to the COD1 families with known \textit{RPGR} mutations, with respect to disease onset and progression and association with myopia.

The clinical features of \textit{COD2} (Xq27.2-q28) are also very similar to those of COD1, although the early stages in \textit{COD2} family members were characterised by peripheral cone...
either a protan (red) defect in colour vision
Both of these cone dysfunctions are congenital and show although no progression to cone-rod dystrophy was observed.
reduced cone responses in ERG, and colour vision defects,
Xq28. These patients also showed decreased visual acuity,
(stub) patients. The diseases described by Reichel
nystagmus was a common sign in blue cone monochromacy
achromatopsia with a little function only in blue cones.
Locus: Xp21.1-11.3 (COD1) may be either COD1 (left column) or the newly described locus (right column)
References: Barley et al., June 2020; Hong et al., July 2020; Seymor et al., August 2020; Brown et al.
General ophthalmological characteristics: Onset within the first three decades and usually before the age of 20,
glacial progression of visual loss, photophobia, moderate to high myopia
Visual fields: Generalised depression in younger patients, central scotomas in older patients, peripheral dysfunction in few cases
Colour vision: Mixed deuteran-titan defect, type I red-green defect, errors with no specific axis, no colour perception in advanced cases
Electroretinogram (ERG): Severe cone dysfunction early in life, moderately reduced rod responses in all age groups
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
Central cone disease progressing to diffuse cone-rod dysfunction: early colour vision impairment with a severity parallel to the degree of visual acuity impairment
Molecular defect (References): Mutations in RPGR exon ORF15 (Demirci et al.,Yang et al.)

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 al8 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, 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 (NX, MIM 300278) and Norrie disease (NDP, MIM 310660) 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 300660), X-linked optic atrophy (OPA1, 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

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

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