Genome-Wide Scan of Exfoliation Syndrome

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Purpose. Exfoliation syndrome (XFS) is an age-related ocular condition that is characterized by the accumulation of fibrillar granular extracellular material in intra- and extracellular tissues. The purpose of the present study was to identify the genetic basis of XFS in a large Finnish family.

Methods. A genome-wide scan with 1000 microsatellite markers was performed in an extended family from an island in the southwestern Finnish archipelago where XFS demonstrates an autosomal dominant mode of inheritance with incomplete penetrance. Two-point linkage analyses were performed with MLINK and multipoint linkage, using the Vitesse program.

Results. Five chromosomal regions with markers showing two-point LOD scores more than 1.5 was identified by using a dominant mode of inheritance for the XFS trait. The most promising locus was assigned to 18q12.1–21.33 with a maximum two-point LOD score of 3.45 and a multipoint LOD score of 4.2. Some evidence of linkage was obtained at chromosomes 2q, 17p, and 19q, which were suggested in earlier reports to be possible regions of linkage to primary open-angle glaucoma (POAG).

Conclusions. The study presented herein offers a starting point to unravel the molecular background of XFS. (Invest Ophthalmol Vis Sci. 2007;48:1436–1442) DOI:10.1167/iovs.06-1092

Exfoliation syndrome (XFS), a risk factor for development and progression of glaucoma,1–3 was first described in 1917 by the Finnish ophthalmologist Lindberg,4 who noted the accumulation of fibrillar granular extracellular debris in ocular tissues in 50% of patients with open-angle glaucoma. Later on, similar material was also detected in many extracellular tissues.5 XFS debris is suggested to be composed of a complex glycopeptide–proteoglycan structure bearing epitopes of the basement membrane, epitopes of elastic fiber system, and components of elastic microfibrils.6 However, the exact composition of XFS material as well as the molecular mechanism responsible for its excessive production and progressive accumulation remains unknown. Pathogenetic factors suggested to influence the abnormal matrix metabolism in the ocular tissues include growth factors, proteolytic enzymes (matrix metalloproteinases [MMPs]) and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]), anterior chamber hypoxia, and increased oxidative stress.6 In total, 23 genes with different expression patterns in the anterior segment tissues of eyes with XFS have recently been reported in a microarray study.7

The prevalence of XFS varies widely among populations, being highest in Scandinavian countries8,9 and Greece,10 but it is almost absent among the Inuits.8 In a population-based study in Finland, the XFS was found in 22% of the population older than 70 years.11 The prevalence increases with age and is highest in the age group between 70 and 80 years.8

Familial aggregation and the increased frequency of XFS in relatives of affected subjects compared with relatives of unaffected subjects12,13 suggest an underlying genetic component.14,15 The main problems with studies on the genetic background of XFS have been the asymptomatic nature of XFS and late age of onset which make it difficult to collect multi-generation families with several affected individuals for linkage and association studies. A wide variety of inheritance models have been suggested depending on the study material15,16 and, of these, the autosomal dominant mode of inheritance with incomplete penetrance has received the most support (Sotirova et al. IOVS 1999;40:ARVO Abstract 512).17,18 Most of these studies investigating XFS inheritance have been based on small pedigrees making hypotheses about the inheritance model uncertain. Thus, only a few molecular genetic studies of XFS have been performed. Loss of heterozygosity (LOH) has been reported on chromosome 13 on locus 13q12.11 and on chromosome 7 on loci 7q13, 7q21.3,18 and 7q21.11,19 in XFS specimens of the iris and anterior capsule. The genetics of primary open-angle glaucoma (POAG) has been studied in greater detail and at least 11 candidate loci (GLC1A–GLC1K) and three predisposing genes—myocilin (MYOC), optineurin (OPTN), and WD repeat domain 36 (WDR36)—have been identified.20 Some of these POAG loci have been excluded for XFS patients.21–24 The purpose of the present study was to identify susceptibility loci for XFS in a large Finnish family originating from a subisolate of the Finnish population in which inheritance of XFS resembles the autosomal dominant model.

Methods

Patient Data

The patient data in the present study were from a population-based study conducted from 1960 to 1962 on an isolated island, Kōkar, in the Åland Archipelago in the southwestern Finnish territory. This island has been permanently inhabited since the 14th century. Five hundred ninety-five subjects older than 10 years (85% of the population) participated in the study. During the subsequent decades, several follow-up studies of the same population were performed; the latest in 2001 and 2002 had 183 participants. Altogether, 530 subjects older than 50 years had undergone ophthalmic examination by the end of 2002.
For all participants, both affected and unaffected, a comprehensive ophthalmic examination was performed including both slit-lamp biomicroscopy and funduscopy, before and after dilatation. XFS was recorded without grading when a grayish central disc, with or without a peripheral band on the anterior lens capsule, and/or fibrillar material on the pupillary ruff was detected (Fig. 1). A subject was recorded as affected (XFS-positive), if XFS was detected in at least one eye. Suspect changes such as Krukenberg’s spindle and pigmentation of cornea endothelium, diffuse haze on the anterior capsule, were noted as negative, and the subject was classified as unaffected. The recorded age of the subjects was the age either when XFS was observed for the first time, or if XFS was not present, the age when the last examination was performed. Diagnosis of glaucoma was based on structural changes in the optic disc (e.g., cup-to-disc ratio ≥ 0.7; localized thinning of the rim, asymmetry ≥ 2 D between the discs), corresponding visual field defect, open anterior chamber angles, and/or intraocular pressure more than 22 mm Hg. Glaucoma without XFS was recorded as POAG and that with XFS as exfoliation glaucoma (XFG).

The study was approved by the Ethics Committee of the Department of Ophthalmology, Central Hospital of Åland, Mariehamn, Finland, and was conducted in accordance with the Declaration of Helsinki. The subjects gave informed consent after explanation of the nature and possible consequences of the study.

Laboratory Procedures
EDTA blood samples were collected from 183 family members who participated in the latest follow-up study. Genomic DNA was extracted from peripheral blood with the standard phenol-chloroform procedure. For mutation screening, PCR and sequencing reactions of the MYOC gene were performed. The HOMOG 3.35 program was used for heterogeneity testing and to calculate the proportion of families showing linkage (a). The ANALYZE program was used to conduct these analyses. Analyses were performed using both dominant (dom) and recessive (rec) models with high penetrance and low phenocopy rate (dom 0.001, 0.999; rec 0.001, 0.001, 0.999) and a rare disease allele frequency (0.0001). Since XFS was prevalent in 14.5% of the Kökar population and we hypothesize that it is a complex disorder, we tested the range of disease allele frequencies accommodating up to 0.14 (0.01, 0.1, 0.14; Supplementary Table S1, online at http://www.iovs.org/cgi/content/full/48/9/4136/DC1). Clinically unaffected family members chosen for the genome scan were scored as unaffected because their mean age at the time of the last examination was 75.3 years (range, 51–94) and because using an affected-only method would have led to substantial loss of information. However, to compare the models affected-only analyses were performed (Supplementary Table S1). The marker allele frequencies were estimated using the DOWNFREQ 2.1 program. Regions with the most promising two-point LOD score results (LOD score, >1.0) were further examined by multipoint analysis with the Vitesse program.

RESULTS
In the cross-sectional part of the study from 1960 to 1962, the prevalence of XFS was 18.4% in 76 subjects older than 70 years. During the period 1960 to 2002, 530 subjects older than 50 years were examined at least once. Of these, 76 were affected with XFS, 23 men, mean age 71.9 years (range, 62–90) and 53 women, mean age 72.3 years (range, 53–88). XFG was found in 24 subjects (11 men, 13 women) and POAG in 12 subjects (7 men, 5 women). Moreover, in the whole population, two women younger than 50 years were affected (one with XFS, one with XFG).

A pedigree was constructed for all XFS-affected subjects. Seventy-five of the 78 who were XFS positive were linked in a large pedigree with 332 examined subjects, in whom the mode of inheritance seemed to resemble an autosomal dominant model. The three most recent generations had been examined several times, but the earlier ones were deceased or unable to participate when the population-based study was conducted. Within this large family, XFS was found in 22% of the examined relatives compared with a 14.5% prevalence in the whole population on the island, suggesting a genetic background.

Among the 183 subjects in the latest follow-up study in 2001 and 2002, 28 had XFS and, of these, 9 had XFG, 7 had POAG, and 148 were unaffected family members.

Mutation Screening
Molecular genetic analyses were started by sequencing the coding region and splice sites of the MYOC gene and the OPTN gene underlying POAG. The first four patients with glaucoma in the latest follow-up study, three with XFG and one with POAG, were chosen for mutation screening. Three patients with XFG had Arg76Lys change in the first exon of the MYOC gene (Fig. 2). This alteration has been considered to be a non-disease-causing polymorphism. No sequence alterations in the MYOC gene were found in the patient with POAG. In the OPTN gene one of the patients with XFG had an Met98Lys alteration in the exon 5 of the gene (Fig. 2). This alteration has been considered to be a non-disease-causing polymorphism. Due to this finding, we sequenced this exon in 70 family members, of whom 18 had XFS, 6 had XFG, 4 had POAG, and 42 were healthy relatives. Thirty-five (18 XFS, 6 XFG, and 11 healthy relatives) individuals of these 70 are also included in the present genome-wide scan. The Met98Lys change was found in one of the two sons and in two nephews of the index case, but not in other family members. None of the mutation carriers, except for the index case, had any symptoms of XFS/XFG or POAG at the time of the examination (age, 40–61 years).

Genome-Wide Scan
From the 183 family members examined in 2001 and 2002, 64 were selected for a genome-wide scan, including all the 28 XFS
The Finnish XFS family. Extended pedigree structure indicating the families included providing material for the genome-wide scan; arrows: sequence alterations in \( \text{OPTN} \) (Arg76Lys) and \( \text{GLC1E} \) (10p15-p14), underlying POAG.20

A genome-wide scan with 1000 microsatellite markers was performed. When the autosomal dominant mode of inheritance with rare disease allele frequency (0.0001) was assumed, seven markers at chromosomal regions 2q32.3, 5q35.3, 17p13.3, 18q12.1-21.33, and Xp22.2 suggested evidence for linkage (\( Z_{\text{max}} > 1.5 \).) In addition, 17 markers at regions 1q, 4p, 4q, 5p, 7p, 7q, 10p, 10q, 13q, 15q, 16q, 19q, Xp, Xq exceeded the highest LOD score using rare disease allele frequency (0.0001; Table 1; Fig. 3) and regions of particular interest for XFS (Table 2) are presented in more detail. The effect of higher disease allele frequencies (0.01, 0.1, 0.14) and an affected-only approach to the LOD scores are demonstrated in Supplementary Table S1.

The most promising chromosomal region was 18q12.1-21.33, where the highest two-point LOD score of 3.45 (\( \theta = 0.04 \) was obtained, with marker \( \text{D18S468} \) assuming the dominant mode of inheritance. Four markers surrounding the best marker exceeded a pair-wise LOD score of 1.0; \( \text{D18S1135} \) (\( Z_{\text{max}} \) dom = 1.39, \( \theta = 0.14, \alpha = 1.00 \), \( \text{D18S450} \) (\( Z_{\text{max}} \) dom = 1.49, \( \theta = 0.08, \alpha = 1.00 \), \( \text{D18S64} \) (\( Z_{\text{max}} \) dom = 1.70, \( \theta = 0.08, \alpha = 0.84 \), and \( \text{D18S1147} \) (\( Z_{\text{max}} \) dom = 1.68, \( \theta = 0.12, \alpha = 0.83 \)) spanning an area of ~30 cM. One allele on the best marker \( \text{D18S468} \) was more often present (37%) in affected than in unaffected (26%) family members, and another allele was found more often in unaffected (34%) than in affected (25%) subjects. Three-point analysis in the best region using adjacent markers \( \text{D18S1102}-\text{D18S468} \), \( \text{D18S468}-\text{D18S1143} \), and \( \text{D18S1143}-\text{D18S450} \) produced maximum multipoint LOD scores of 1.85 (\( \theta = 0.03; 0.10 \), 2.28 (\( \theta = 0.08; 0.05 \)), and 1.73 (\( \theta = 0.15; 0.05 \)), respectively. When we combined the information from markers \( \text{D18S1135} \) and \( \text{D18S468} \), located 5 cM apart, the maximum threepoint LOD score was 2.80 (\( \theta = 0.05; 0.10 \), and using markers \( \text{D18S468} \) and \( \text{D18S450} \), located 8 cM apart, the highest three-point LOD score of 4.33 (\( \theta = 0.05; 0.08 \)) was obtained. The complete results for three-point analysis over the region are shown in Table 3.

Two markers, \( \text{D4S2936} \) and \( \text{D4S394} \), situated 14 cM apart at region 4p16.1-16.3, resulted in slightly positive pair-wise LOD scores (\( Z_{\text{max}} > 1.0 \)) (Table 1) and with adjacent markers \( \text{D4S2936}-\text{D4S412} \) and \( \text{D4S2935}-\text{D4S394} \) multipoint LOD scores of 1.07 (\( \theta = 0.15; 0.04 \) and 1.51 (\( \theta = 0.10; 0.019 \)) were obtained, respectively. The singleton marker \( \text{D10S602} \) at 10p15.3 produced a slightly positive two-point LOD score (\( Z_{\text{max}} > 1.0 \); Table 1) and adjacent markers \( \text{D10S602}-\text{D10S1218} \) yielded a maximum three-point LOD score of 1.22 (\( \theta = 0.10; 0.05 \). It is noteworthy that marker \( \text{D10S602} \) resides next to the \( \text{GLC1E} \) locus (10p15-p14), underlying POAG.20

The highest pair-wise LOD score on chromosome 2 was obtained with marker \( \text{D2S117} \) (\( Z_{\text{max}} \) dom = 1.73, \( \theta = 0.06, \alpha = 1.00 \)) at region 2q32.3. Multipoint analysis with the adjacent markers \( \text{D2S117} \) and \( \text{D2S311} \) produced a three-point LOD score of 1.21 (\( \theta = 0.10; 0.05 \)). Suggestive evidence of linkage was also observed on chromosome 17 with marker \( \text{D17S849} \) (\( Z_{\text{max}} \) dom = 1.91, \( \theta = 0.04, \alpha = 1.00 \)), on chromosome 5 with marker \( \text{D5S2049} \) (\( Z_{\text{max}} \) dom = 1.61, \( \theta = 0.00, \alpha = 1.00 \)), and on chromosome 19 with marker \( \text{D19S932} \) (\( Z_{\text{max}} \) dom = 1.09, \( \theta = 0.00, \alpha = 0.92 \)).
A nominal linkage (two-point LOD score, >1.0) was observed at regions 7q21.3 with marker D7S554 and 7p12.3 with marker D7S2506, assuming an autosomal recessive mode of inheritance (Table 1). Marker D15S1032 produced an individual positive LOD score (\(Z_{max}\)) at location 15q21.2 (Table 1). At chromosome region 16q12.2, marker D16S3034 (\(Z_{max} = 1.35, \theta = 0.12, \alpha = 1.00\)) exceeded the threshold LOD score of 1.0 and, together with adjacent marker D16S415, a three-point LOD score of 1.33 (\(\theta = 0.20; 0.01\)) was produced.

On chromosome X the highest pair-wise LOD scores were observed at DXS7108 (\(Z_{max} = 1.52, \theta = 0.12, \alpha = 1.00\)) and DXS6810 (\(Z_{max} = 1.18, \theta = 0.10, \alpha = 1.00\)) lying ~50 cM apart (Table 1).

### DISCUSSION

A genome-wide scan was performed in 64 subjects from one large pedigree; of these, 28 were XFS/XFG affected and 36 were unaffected. The most promising locus was at 18q12.1-21.33, where several markers, using both rare and common disease allele frequencies, gave evidence of linkage (Supplementary Table S1). The other interesting loci were 2q32.3, 7p12.3, 7q21.3, 15q21.2, 16q12.2, 17p13.3, 19q12, and Xp11.3. The locus, 18q12.1-21.33, on chromosome 18 is considerable in size (~30 cM). The annotated human sequence makes it possible to compile a comprehensive list of candidate genes in the region. This locus includes numerous genes with both known and unknown functions. Most of these genes are also expressed in ocular tissues at some level. Chromosome 18 has not been reported to be associated with either XFS or POAG and thus the finding at 18q12.1-21.33 provides evidence of a novel XFS susceptibility locus on this chromosome. Though so far XFS is the most common identifiable cause of POAG, we were also interested in determining whether the loci identified for XFS are situated in regions that overlap the loci earlier associated with POAG.

**Table 1. Highest Two-Point LOD Scores**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Location</th>
<th>Position (cM)</th>
<th>Model</th>
<th>(Z_{max})</th>
<th>(\theta)</th>
<th>(\alpha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D15S245</td>
<td>1q32.2</td>
<td>217</td>
<td>Rec</td>
<td>1.098</td>
<td>0.00</td>
<td>1.00</td>
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<td>D2S117</td>
<td>2q32.3</td>
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<td>Dom</td>
<td>1.725</td>
<td>0.06</td>
<td>1.00</td>
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<td>D4S2936</td>
<td>4p16.3</td>
<td>0.9</td>
<td>Dom</td>
<td>1.000</td>
<td>0.00</td>
<td>0.61</td>
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<td>D4S394</td>
<td>4p16.1</td>
<td>15</td>
<td>Dom</td>
<td>1.328</td>
<td>0.10</td>
<td>1.00</td>
</tr>
<tr>
<td>D6S26</td>
<td>4q35.2</td>
<td>202</td>
<td>Dom</td>
<td>1.253</td>
<td>0.14</td>
<td>1.00</td>
</tr>
<tr>
<td>D5S2031</td>
<td>5p14.3</td>
<td>42</td>
<td>Rec</td>
<td>1.185</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>D5S2049</td>
<td>5q33.3</td>
<td>166</td>
<td>Dom</td>
<td>1.605</td>
<td>0.00</td>
<td>1.00</td>
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<td>Rec</td>
<td>1.253</td>
<td>0.00</td>
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<tr>
<td>D7S554</td>
<td>7q21.3</td>
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<td>Rec</td>
<td>1.126</td>
<td>0.00</td>
<td>1.00</td>
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<td>Dom</td>
<td>1.284</td>
<td>0.08</td>
<td>1.00</td>
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<td>D10S192</td>
<td>10q24.1</td>
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<td>1.295</td>
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<td>10q26.2</td>
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<td>Dom</td>
<td>1.398</td>
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<tr>
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<td>Dom</td>
<td>1.491</td>
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<td>Dom</td>
<td>1.695</td>
<td>0.08</td>
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<td>D18S1147</td>
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<td>Dom</td>
<td>1.682</td>
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<td>19q12</td>
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<td>Dom</td>
<td>1.086</td>
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</table>

Markers with \(Z_{max} > 1.0\), using dominant (Dom: 0.001, 0.999, 0.999) or recessive (Rec: 0.001, 0.001, 0.999) mode of inheritance and a rare disease allele frequency (0.0001), are presented. The LOD scores are maximized over recombination fractions (\(\theta\)) ranging from 0 to 0.5. \(\alpha\) ranging from 0 to 1.0 indicates the proportion of families showing linkage. The markers with \(Z_{max} > 1.5\) are shown in bold.
highest-scoring regions for adult onset POAG in Wiggs et al.40 situated at loci 17p13.3 and 19q12, which are two of the POAG. This marker produced a two-point LOD score of 1.97 located on the previously suggested candidate region for chromosome 19 with marker D17S849 (LODHom) are maximized over recombination fractions (θ) ranging from 0 to 0.5, whereas heterogeneity LOD scores (LODHet) yielding the highest LOD score (Z_{max}) are shown. The best multipoint LOD scores can also be found in the table.

Markers with pair-wise LOD score >1.0 in the current study are presented.

On chromosome 2, the highest pair-wise LOD score was obtained with marker D2S117 at region 2q32.3. D2S117 is located on the previously suggested candidate region for POAG. This marker produced a two-point LOD score of 1.97 using the dominant inheritance model in the original genome-wide scan of POAG.39 Suggestive evidence of linkage was also observed on chromosome 17 with marker D17S849 and on chromosome 19 with marker D19S932. These two markers are situated at loci 17p13.3 and 19q12, which are two of the highest-scoring regions for adult onset POAG in Wiggs et al.40 In that study, marker D17S926, which overlapping marker D17S849, produced a maximum pair-wise LOD score of 2.25 and marker D19S932, residing 5 cM from D19S932, resulted in Z_{max} = 3.11, assuming an autosomal recessive mode of inheritance. These findings suggest the possibility of some shared factors behind XFS and POAG. It is noteworthy that the apolipoprotein E (ApoE) gene, which has been reported to be associated with the development of XFS37 and to participate in amyloid deposition and fibril formation, is located some distance away from D19S932, at 19q13.31.

A nominal linkage was observed at regions 7p12.3 with marker D7S2506 and 7q21.3 with marker D7S554. These regions are the nearby regions 7p13, 7q21.3, and 7q21.11, where a loss of heterozygosity in XFS specimens has been reported with markers D7S478, D7S479,18 and D7S820,19 respectively. Chromosome 7 is also of interest because it carries gene sequences encoding elastin (at 7q11.23), laminin B1 (7q31.1), and collagen 1A2 (7q21.3), especially as XFS is commonly recognized as a type of elastosis.

An individual positive LOD score was produced at region 15q21.2 with marker D15S1032, which is situated approximately 8 cM from the fibrillin-1 at locus 15q21.1. Fibrillin-1 is an intrinsic component of elastic microfibris and XFS fibers8 and has been observed to be upregulated in ciliary processes, iris tissue, and the lens epithelium of XFS-affected eyes.7

At chromosome location 16q12.2, marker D16S3034 exceeded the threshold LOD score of 1.0 and is situated at the same chromosome arm as MMP2 (at 16q13), a major MMP in human aqueous humor that cleaves type IV collagen. The slightly positive marker DXS6810 at chromosome region Xp11.3 lies next to TIMP1 (at Xp11.3-11.23), the endogenous inhibitor of MMP-1 and -9. Elevated TIMP-2 (tissue inhibitor of MMP-2) and low MMP-2 levels, as well as an excess of TIMP-1 over MMP-9,38 in the aqueous humor of XFS eyes and upregulation and increased production of TIMP-2 and a contrasting downregulation of TIMP-1 in anterior segment tissues of eyes with XFS7 has been reported in previous studies. Excessive TIMPs have been suggested to prevent the destruction of newly synthesized matrix, leading to exfoliate accumulation.38 Further studies are needed to confirm the role of the MMP/TIMP pathway in the pathophysiology of XFS.

No hint of linkage was obtained for markers at 1p13.2, near adenosine receptor A3 (ADOR3), which participates in aqueous humor secretion and IOP regulation, for example, and whose mRNA and protein have been found to be significantly upregulated in the nonpigmented ciliary epithelium of XFS/ XFG eyes.7,41 No evidence for linkage was identified either in loci 2p14-2cen or 2q35-q36, which have been suggested to be putative candidate loci for XFS (Sotirova et al. IOVS 1999:40 ARVO Abstract 512).

The main problem with investigations of late-onset diseases is recruitment of affected individuals in several subsequent generations. In the family in the present study, detailed phe-
notypes are available from three generations. The mean age of unaffected family members included in the study at the time of the last examination was 75.3 years (range, 51–94). Approximately one fifth of examined family members are likely to be affected during their lifetimes; and, correspondingly, approximately 80% of the unaffected will stay unaffected. Therefore, we accepted a model in which the unaffected were scored as unaffected in linkage analyses. However, we also calculated two-point LOD score results obtained by marking all unaffected family members as unknown in the linkage analysis (Supplementary Table S1). Although there is some variation in LOD scores, as expected, depending on the model, the loci remain the same.

The isolated island of Kökar offered a good starting point for genetic studies. Its small population made it possible to examine nearly all the inhabitants, and they were interested in the follow-up examinations. We hypothesize that widespread genetic and environmental homogeneity may make it easier to identify common predisposing alleles that are identical by descent (IBD). Because of the isolated location of the island, the founder effect cannot be excluded, although the prevalence of XFS is high in the elderly in the mainland of Finland (22%) and in Kökar (18.4%). Bearing in mind the high prevalence of XFS in Kökar and the possibility that rare alleles could have been enriched in this small, isolated population we examined the effect of disease allele frequency on LOD scores by using the range of disease allele frequencies accommodating up to 0.14 (0.0001, 0.01, 0.1, 0.14; Supplementary Table S1). We assume that XFS is caused by several predisposing genes, with an unknown allele frequency for each of them. Because of the complex nature of the disease, the true disease allele frequency is probably less than 0.14. Although, most of the subfamilies of the original family in the present study were linked to the same genetic loci (α = 1.0), there were also markers where only some of the families were linked (α < 1.0; Table 1). This evidence implies that other genetic loci and predisposing alleles are needed for the expression of the XFS phenotype in this subisolate. We assume that one major gene is responsible for XFS in our family, although we cannot exclude the impact of other susceptibility genes. This explanation may be due to high frequency and the multifactorial nature of the disease and the import of new alleles by married-ins in the pedigree. Heterogeneity demonstrated in the present study, as well as candidate genes and regions represented in previous investigations (Sotirova et al. IOVS 1999;40:ARVO Abstract 512), support the idea that multiple genes underlie XFS.

In conclusion, the most promising locus was assigned to chromosome 18q12.1-21.33. Markers on chromosomes 2, 17, and 19 producing positive signals overlap the previously suggested possible regions of POAG linkage. This finding leads to the question of whether there are possible common predisposing alleles. Further investigations of the regions in these two different phenotypes are warranted.

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References


