Nonsyndromic High Myopia in a Chinese Family Mapped to MYP1

Linkage Confirmation and Phenotypic Characterization

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Objective: To identify the genetic locus for X-linked nonsyndromic high myopia in a large Chinese family.

Methods: Phenotypic information and DNA samples were collected from 19 individuals in a Chinese family; 7 had high myopia and 12 were unaffected. We performed a linkage scan on the X chromosome and sequenced several candidate genes.

Results: High myopia in this family, presenting since early childhood and ranging from −6.00 to −15.00 diopters of sphere, is consistent with an X-linked recessive trait. The presence of a normal optic disc and the absence of color visual defects and other systemic abnormalities indicated that high myopia in this family is nonsyndromic. Our linkage analysis mapped the disease locus to Xq28, a 6.1-cM region between DXS8069 and Xqter, with 2-point logarithm of odds scores greater than 2.0 for 5 markers and a maximum logarithm of odds score of 3.59 at θ = 0 for 2 markers. Sequence analysis of coding and adjacent intronic regions of GPR50, PRRG3, CNGA2, and BGN did not identify any potential causative mutation.

Conclusions: Nonsyndromic high myopia in a Chinese family was mapped to the MYP1 region, which confirmed and refined this region for high myopia. In addition, our results suggest that color visual defects and optic disc hypoplasia are not necessary signs of high myopia attributed to the MYP1 region.

Clinical Relevance: MYP1 is a common and the best locus for positional cloning of the gene responsible for high myopia. Our results suggest that MYP1 is also responsible for nonsyndromic high myopia.


Myopia is the leading cause of visual impairment, and complications associated with high myopia are the most common causes of irreversible blindness. In several studies, genetic factors have been shown to play an important role in the development of high myopia. Both mendelian and complex modes of inheritance have been suggested but the genes responsible for most cases of high myopia have not been identified.

A number of genetic loci for mendelian high myopia have been identified including 1 locus that is responsible for autosomal recessive high myopia (MYP1), 2 loci for X-linked high myopia (MYP1, MYP2), 2 loci for autosomal dominant high myopia (MYP2, MYP5, MYP6), and 8 loci for autosomal dominant high myopia (MYP1, MYP2, MYP3, MYP4, MYP5, MYP11, MYP12, MYP15, MYP16). However, most loci for high myopia have not been independently confirmed by a separate study or by studying families from different ethnic groups. As high myopia is common (its frequency ranges from 1.8% to 8.2% in the East Asian population), spurious signals could arise during linkage mapping when pedigrees segregating for high myopia contain individuals who are phenotypically similar but carry different disease alleles. In addition, as myopia is genetically heterogeneous, an individual with complex high myopia may not be properly identified in a linkage study for mendelian high myopia if the affected status is not properly defined. Such problems might have contributed to the lack of success in cloning myopia genes thus far. Therefore, independent confirmation and further refinement of genetic loci would be critical for the identification of causative genes for high myopia.

The first locus for high myopia, MYP1 (OMIM 310460), which was mapped to Xq28 based on a linkage study of a Danish family in 1990, is associated with optic disc hypoplasia and colorblindness. An independent linkage study on another Danish family with a similar X-linked phenotype also mapped to the same region. MYP1 has been considered as a locus for syndromic high myopia owing to its association with optic disc hypoplasia and color-
blindness. However, a locus for X-linked nonsyndromic high myopia, MYP13, is located nearby. Therefore, it would be interesting to see if the MYP1 region could be responsible for X-linked nonsyndromic high myopia in other families. In this study, we observed linkage to X-linked high myopia in a Chinese family at Xq28. This result both confirmed and further refined the MYP1 region in a different ethnic group compared with previous studies.

**METHODS**

The family included in this study lives in Guangxi province, China, and is of Chinese Han descent. Seven affected men and 12 unaffected individuals across 3 generations participated in this study. Written informed consent conforming to the tenets of the Declaration of Helsinki and following the Guidance of Sample Collection of Human Genetic Diseases (863...
RESULTS

All 7 affected men had significant myopia before school age but did not have color visual defects, night blindness, or photophobia. Pedigree analysis demonstrated a typical pattern of an X-linked recessive trait (Figure 1). Six of the 7 affected men had myopia that ranged from −6.00 diopters of sphere (DS) to −15.00 DS (Table 1). Refraction for 1 affected man (patient II:5) was not available owing to senile cataract, although significant nearsightedness was present in this individual since early childhood. Refractive errors for 11 of the 12 unaffected individuals were between −2.00 DS and +0.50 DS. The other unaffected individual (patient III:5), an obligate carrier, had myopia of −3.50 diopters (D) OD and −6.75 D OS. Ophthalmologic and systemic examination of all patients did not identify any signs that suggest syndromic high myopia. Owing to significant myopic fundus changes in 6 of the 7 affected men (fundi were not visible for patient II:5 owing to senile cataract), affected and unaffected individuals could be differentiated by ophthalmoscopic examination (Figure 2). An exception is the obligate carrier (patient III:5) who had myopic fundus change in her left eye, possibly due to uneven Lyonization or skewed X inactivation.42,43 Electroretinographic recordings in 3 men with high myopia revealed reduced amplitude of cone response (Figure 3). All 19 participants in this study had normal color vision except for 1 (patient II:5) who was unable to take the color vision test owing to senile cataracts.

An initial X chromosome–wide linkage scan excluded all X chromosome regions except Xq28. Genotyping of additional microsatellite markers between DXS8069 (at 149.39 Mb) and DXS1073 (at 153.48 Mb), including DXS8103 (at 149.87 Mb), DXS8061 (at 151.77 Mb), and DXS8087 (at 152.55 Mb), were uninformative. Sequence analysis of the GPR50, PRRG3, CNGA2, and BGN genes located in the region between DXS8069 and DXS1073 failed to detect any causative mutation (Table 2). However, we detected sequence variants in these genes that could serve as informative markers for linkage analysis. Fine mapping based on sequence variants in

### Table 1. Clinical Data of the Family Members Who Participated in the Study

<table>
<thead>
<tr>
<th>Patient ID/ Sex/Age, y</th>
<th>Education, y</th>
<th>Status</th>
<th>Age at First Symptom, y</th>
<th>Uncorrected (Corrected)</th>
<th>Refraction</th>
<th>Fundus OD/OS</th>
<th>Axial Length OD/OS, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD/OS</td>
<td>OD/OS</td>
<td>OD/OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II:1/F/68 1</td>
<td>1</td>
<td>Unaffected</td>
<td>...</td>
<td>HM/10 cm 0.25</td>
<td>NA</td>
<td>−2.00 DS-0.50 DC</td>
<td>NA/Unaffected</td>
</tr>
<tr>
<td>II:2/M/70 2</td>
<td>2</td>
<td>Unaffected</td>
<td>...</td>
<td>0.8</td>
<td>1</td>
<td>0.50 DS-0.75 DC</td>
<td>0.75 DS-0.50 DS</td>
</tr>
<tr>
<td>II:3/M/78 3</td>
<td>3</td>
<td>Unaffected</td>
<td>...</td>
<td>0.4 (0.8) 0.4 (0.8)</td>
<td>−1.25 DS-0.75 DS</td>
<td>−0.50 DS-2.00 DS</td>
<td>Unaffected</td>
</tr>
<tr>
<td>II:5/M/75 6</td>
<td>6</td>
<td>Affected</td>
<td>&lt;7</td>
<td>1.2</td>
<td>1.2</td>
<td>−0.25 DC</td>
<td>0</td>
</tr>
<tr>
<td>II:1/F/43 9</td>
<td>9</td>
<td>Unaffected</td>
<td>...</td>
<td>1.2</td>
<td>1.2</td>
<td>−0.50 DC</td>
<td>−0.50 DS</td>
</tr>
<tr>
<td>II:2/M/47 9</td>
<td>9</td>
<td>Unaffected</td>
<td>...</td>
<td>1.2</td>
<td>1.2</td>
<td>−0.50 DS</td>
<td>−0.50 DS</td>
</tr>
<tr>
<td>II:5/F/33 5</td>
<td>5</td>
<td>Unaffected</td>
<td>11</td>
<td>0.3 (0.9) 0.1 (0.3)</td>
<td>−3.25 DS-0.75 DC</td>
<td>−6.25 DS-1.00 DC</td>
<td>Unaffected/myopic</td>
</tr>
<tr>
<td>II:6/M/30 9</td>
<td>9</td>
<td>Unaffected</td>
<td>...</td>
<td>1.2</td>
<td>1.2</td>
<td>−0.50 DS</td>
<td>−0.50 DC</td>
</tr>
<tr>
<td>II:7/M/22 7</td>
<td>7</td>
<td>Unaffected</td>
<td>...</td>
<td>1.5</td>
<td>1.5</td>
<td>−0.50 DC</td>
<td>−0.50 DC</td>
</tr>
<tr>
<td>II:8/F/48 4</td>
<td>4</td>
<td>Unaffected</td>
<td>...</td>
<td>1.2</td>
<td>1.2</td>
<td>0.50 DS</td>
<td>0.5 DS</td>
</tr>
<tr>
<td>III:10/M/26 9</td>
<td>9</td>
<td>Unaffected</td>
<td>...</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV:1/M/19 9</td>
<td>9</td>
<td>Affected</td>
<td>&lt;7</td>
<td>0.1 (0.8) 0.03 (0.6)</td>
<td>−6.00 DS-3.25 DC</td>
<td>−6.25 DS-3.25 DC</td>
<td>Myopic</td>
</tr>
<tr>
<td>IV:2/M/12 5</td>
<td>5</td>
<td>Affected</td>
<td>&lt;7</td>
<td>0.2 (0.6) 0.1 (0.8)</td>
<td>−8.25 DS-2.25 DC</td>
<td>−9.00 DS-1.25 DC</td>
<td>Myopic</td>
</tr>
<tr>
<td>IV:3/M/12 5</td>
<td>5</td>
<td>Affected</td>
<td>&lt;7</td>
<td>0.1 (0.5) 0.1 (0.5)</td>
<td>−9.25 DS-1.25 DC</td>
<td>−9.25 DS-0.75 DC</td>
<td>Myopic</td>
</tr>
<tr>
<td>IV:4/M/6 0</td>
<td>6</td>
<td>Affected</td>
<td>&lt;6</td>
<td>0.2</td>
<td>0.3</td>
<td>−10.50 DS-1.25 DC</td>
<td>−10.50 DS-1.75 DC</td>
</tr>
<tr>
<td>IV:5/M/31 6</td>
<td>6</td>
<td>Affected</td>
<td>&lt;6</td>
<td>0.05 (0.7) 0.02 (0.5)</td>
<td>−15.00 DS-1.50 DC</td>
<td>−15.00 DS-1.75 DC</td>
<td>Myopic</td>
</tr>
<tr>
<td>IV:6/M/29 3</td>
<td>3</td>
<td>Unaffected</td>
<td>...</td>
<td>1.5</td>
<td>1.5</td>
<td>−0.50 DC-0.50 DC</td>
<td>Unaffected</td>
</tr>
<tr>
<td>IV:7/M/14 8</td>
<td>8</td>
<td>Affected</td>
<td>&lt;6</td>
<td>0.1 (0.6) 0.1 (0.6)</td>
<td>−9.25 DS-1.25 DC</td>
<td>−10.25 DS-1.50 DC</td>
<td>Myopic</td>
</tr>
</tbody>
</table>

Abbreviations: DC, diopters of cylinder; DS, diopters of sphere; ellipses, no myopia symptom; HM, hand movement; LP, light perception; NA, not available. aUnable to measure owing to senile cataract.
GPR50, PRRG3, CNGA2, and BGN established highly significant linkage, with a 2-point logarithm of odds (LOD) score greater than 2.0 for 5 variants and a maximum 2-point LOD score of 3.59 at $\theta=0$ obtained for variants in PRRG3 and CNGA2 (Table 3). A haplotype analysis and the presence of a critical recombinant in individual IV:7 at DXS8069 further refined the critical interval to the region between DXS8069 and the telomere of Xq (Figure 1). The telomeric boundary of the candidate interval remains unknown. Therefore, the high myopia candidate interval is located in a 5.61-Mb region on Xq28 between DXS8069 and Xqter.
In this study, X-linked high myopia in a Chinese family is mapped to the MYP1 region between DXS8069 and Xqter. A 2-point LOD score over 2.0 at \( \theta = 0 \) for 5 polymorphic markers and a maximum LOD score of 3.59 at \( \theta = 0 \) established highly significant linkage of myopia to Xq28 based on the conventional criteria for X-linked disease.44,45 The exclusion of other regions on the X chromosome by linkage analysis (including the MYP13 region), a maximum 2-point LOD score of 3.59, and a haplotype analysis all suggest that the MYP1 region is responsible for high myopia in this family.

Two loci, MYP1 and MYP13, have been previously identified to cause X-linked recessive high myopia.18,27,31,39 The linkage interval of the current myopia locus is about 25.99 Mb away from MYP13, located at Xq25-q27.2 between DXS1210 and DXS805718 and about 5.55 Mb away from the linkage interval between DXS8059 and DXS8043, which support MYP13.39 Earlier studies had mapped the MYP1 locus to a region distal to DXS8103.27,31 In this study, we established linkage to the MYP1 region and refined the proximal boundary from DXS8103 to DXS8069.

A novel finding from this study is that the clinical phenotypes from the Chinese family indicate a nonsyndromic form of high myopia. Our previous linkage studies had mapped this phenotype to the MYP11, MYP13, and MYP18 regions.11,18,19,39 This nonsyndromic high myopia phenotype is distinct from 2 Danish families that mapped to MYP1, ie, the family with Bernholm Eye Disease and the Minnesota family.27,31 Affected individuals in the family with Bornholm eye disease had deuteranopia and hypoplasia of optic disc, and those in the Minnesota family had protanopia. These previous findings raised the question about whether MYP1 represents a locus for syndromic or nonsyndromic high myopia. Nevertheless, patients in all 3 families mapped to the MYP1 locus share many common features seen in nonsyndromic high myopia. Most importantly, the onset of high myopia occurs earlier in life in the Chinese family than it does in the 2 Danish families.

### Table 3. Two-Point Linkage Results for Markers in the X Chromosome

<table>
<thead>
<tr>
<th>Markers</th>
<th>cM/Gene</th>
<th>Mb</th>
<th>Position</th>
<th>Logarithm of Odds Score, ( \theta )</th>
<th>Maximum z Score</th>
<th>Maximum ( \theta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXS1227</td>
<td>164.70</td>
<td>140.63</td>
<td>-4.46</td>
<td>-2.47</td>
<td>-1.71</td>
<td>-1.09</td>
</tr>
<tr>
<td>DXS8106</td>
<td>173.60</td>
<td>142.01</td>
<td>-3.32</td>
<td>-1.33</td>
<td>-0.57</td>
<td>0.03</td>
</tr>
<tr>
<td>DXS8084</td>
<td>174.70</td>
<td>142.60</td>
<td>-1.33</td>
<td>-0.07</td>
<td>0.34</td>
<td>0.54</td>
</tr>
<tr>
<td>DXS8043</td>
<td>176.70</td>
<td>143.84</td>
<td>1.38</td>
<td>1.86</td>
<td>1.87</td>
<td>1.54</td>
</tr>
<tr>
<td>DXS8045</td>
<td>179.80</td>
<td>145.32</td>
<td>-0.43</td>
<td>0.28</td>
<td>0.55</td>
<td>0.67</td>
</tr>
<tr>
<td>DXS1139</td>
<td>187.18</td>
<td>149.19</td>
<td>1.56</td>
<td>2.02</td>
<td>2.02</td>
<td>1.66</td>
</tr>
<tr>
<td>DXS8069</td>
<td>190.40</td>
<td>149.39</td>
<td>1.86</td>
<td>2.32</td>
<td>2.32</td>
<td>1.96</td>
</tr>
<tr>
<td>rs68058591</td>
<td>GPR50A</td>
<td>150.10</td>
<td>2.81</td>
<td>2.76</td>
<td>2.55</td>
<td>2.29</td>
</tr>
<tr>
<td>rs561077d</td>
<td>GPR50B</td>
<td>150.10</td>
<td>2.83</td>
<td>2.78</td>
<td>2.58</td>
<td>2.31</td>
</tr>
<tr>
<td>rs3827429</td>
<td>PRRG3</td>
<td>150.62</td>
<td>3.59</td>
<td>3.53</td>
<td>3.28</td>
<td>2.96</td>
</tr>
<tr>
<td>rs35350051f</td>
<td>CNGA2</td>
<td>150.66</td>
<td>3.59</td>
<td>3.53</td>
<td>3.28</td>
<td>2.96</td>
</tr>
<tr>
<td>rs1126499g</td>
<td>BGN</td>
<td>152.42</td>
<td>2.69</td>
<td>2.65</td>
<td>2.47</td>
<td>2.24</td>
</tr>
<tr>
<td>DXS1073</td>
<td>196.50</td>
<td>153.48</td>
<td>1.54</td>
<td>1.55</td>
<td>1.48</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Abbreviation: SNP, single-nucleotide polymorphism.

a Genethon map.

b Genome Build 36.3.

c rs68058591 is located in GPR50A, exon 2, at gDNA 150 100 227 base pairs (bp).

d rs561077 is located in GPR50B, exon 2, at gDNA 150 100 307 bp.

e rs3827429 is located in PRRG3, exon 1, at gDNA 150 617 725 bp.

f rs35350051 is located in CNGA2, exon 5, at gDNA 150 659 963 bp.

g rs1126499 is located in BGN, exon 2, at gDNA 152 424 703 bp.
myopia occurred in early childhood, thereby suggesting minimal environmental interference and providing an ideal model for studying mendelian high myopia. 

As high myopia may be transmitted either as a mendelian or a complex trait and no genes have been identified for nonsyndromic high myopia, confirmation and refinement of myopia loci would be a major step toward identifying causative genes. An important result from our study is that high myopia in the Chinese family was mapped to the MYP1 locus, which confirmed and refined the candidate interval for MYP1. This is the first high myopia locus where highly significant evidence is obtained from a large family of a different ethnic origin than previously studied. To date, MYP1 is the only locus that has been independently confirmed by 3 separate studies using linkage analysis. Several other mapped loci were also confirmed in replication studies; however, such evidence was obtained either using the same ethnic population (such as MYP3 and MYP1) or the study did not obtain conclusive evidence of genetic linkage. Therefore, the confirmation and refinement of a genetic locus provides a major step toward understanding the molecular mechanism of genetically heterogeneous diseases such as high myopia.

There were about 151 genes in the linkage interval distal to DXS8069. We selected candidate genes for sequencing that were expressed in the eye or functionally related to genes responsible for eye diseases and had no known disease association. Unlike retinitis pigmentosa in which genes involved in the visual cycle or functionally related to known causative genes may be good candidates, it is difficult to identify candidate genes for high myopia. This is because the genetic lesions for nonsyndromic high myopia have not been identified and the molecular mechanism for human myopia is unknown. The 4 candidate genes that we sequenced were GPR50, PRRG3, CNGA2, and BGN. GPR50 encodes a G protein–coupled receptor that plays an important role in mediating the intracellular effects of neurotransmitters and hormones; it is also expressed in the retina. PRRG3 encodes a proline-rich 2-hydroxyglutamic acid protein and is expressed in retina. CNGA2 encodes a protein for cyclic nucleotide-gated channel proteins that are essential in visual and olfactory signal transduction. Mutations in CNGA1, another member of cyclic nucleotide-gated channel proteins, are responsible for retinitis pigmentosa. BGN encodes a small proteoglycan present in many connective tissues and is also expressed in the eye.

In summary, our study confirmed and refined the MYP1 candidate region. Our results suggest that MYP1 is also responsible for nonsyndromic high myopia and is a common locus for high myopia in different ethnic groups. As such, MYP1 might be an excellent candidate locus for identifying a causative gene for high myopia.

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