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SHORT COMMUNICATION

# Confirmation of a genetic locus for X-linked recessive high myopia outside MYP1

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**Abstract** High myopia is a severe ocular condition affecting ~100 million people throughout the world. It is a common cause of blindness, and several studies have suggested it is transmitted through Mendelian traits. High myopia is clinically and genetically heterogeneous, with eight loci assigned. Most loci have not been confirmed by additional studies, and genes responsible for high myopia have not been identified. We recently studied a Chinese family with X-linked high myopia and mapped the high myopia locus to Xq25-q27.2. This linked region overlapped with that of MYP13 but was outside MYP1.

**Keywords** High myopia · X-linked recessive · Linkage analysis · Locus · MYP1 · MYP13 · Gene

## Introduction

High myopia, the extreme form of myopia, is the fourth most common cause of irreversible blindness, predominantly because of associated complications including vision-threatening retinal detachment and macular degeneration (Paluru et al. 2003; Pararajasegaram 1999). High myopia is usually regarded as hereditary—as an autosomal dominant, autosomal recessive, or X-linked recessive trait. Some high myopia might be inherited in a complex fashion. So far, eight loci for high myopia have been reported, including MYP1 (Xq28) (Young et al. 2004), MYP2 (18p11.31) (Young et al. 1998b), MYP3 (12q21-q23) (Young et al. 1998a), MYP4 (7q36) (Naiglin et al. 2002), MYP5 (17q21-q22) (Paluru et al. 2003), MYP11 (4q22-q27) (Zhang et al. 2005), MYP12 (2q37.1) (Paluru et al. 2005), and MYP13 (Xq23-q25) (Zhang et al. 2006). Different genetic loci have been mapped in different populations, and none of the responsible genes has been identified. Identification of genes responsible for high myopia should be a priority in the overall effort toward understanding, prevention, and treatment of this disease. Verification and confirmation of those mapped loci would be an important step toward identification of such genes.

As part of our ongoing projects to identify the genetic cause of high myopia, a Chinese family containing six males affected by high myopia was studied. An X-chromosome genome-wide linkage study was performed and the myopia in the family was mapped to Xq25-q27.2, which overlapped with MYP13 but was outside MYP1.

## Methods

The family studied is of Chinese Han ethnicity living in Guangdong province, China. Seventeen individuals, including six affected and eleven unaffected, participated in the study. Informed consent conforming with the tenets of the Declaration of Helsinki and following the Guidance of Sample Collection of Human Genetic Diseases (863-Plan) of the Ministry of Public Health of China was obtained from the participating individuals before the study and the study was approved by the Institutional Review Boards of the Zhongshan Ophthalmic Center. Medical and ophthalmic histories were obtained, and ophthalmological examination was performed (by Drs Zhang and Guo).

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Refractive error was measured by retinoscopy. Criteria for high myopia are the same as described previously (Zhang et al. 2006). Electroretinogram (ERG) responses were recorded for two affected members consistent with ISCEV standards (Anonymous 1989). Color vision was evaluated by using the Ishihara plate and by analyzing exon 5 of the red–green gene array, as described previously (Zhang et al. 2006; Zhang and Minoda 1996).

Genotyping and linkage analysis were performed as described previously (Guo et al. 2006; Zhang et al. 2006). Fluorescein-labeled microsatellite markers from ABI (Applied Biosystems, Foster City, CA, USA) were used for genotyping.

## Results

The family described in this study lives in a mountain village approximately 500 km from Guangzhou, China. The pedigree demonstrated the typical pattern of the X-linked recessive trait (Fig. 1). Myopia in six affected members ranged from –7.00 to –16.00 D. All affected individuals developed myopia before school. No patient had night blindness or photophobia. Refractive error for unaffected members of the family was between –1.00 and +1.00 D except for individuals II:1 and II:2. Individual II:1 had immature senile cataract with refraction of –2.50 D (OD) and –3.50 D (OS). The refractive condition for individual II:2 was not measured because of mature senile cataract. Individuals II:1 and II:2 did not have noticeable nearsightedness before they developed cataract. Ophthalmological examination excluded known ocular diseases associate with myopia. All affected individuals had temporal crescent of the optic disc and thinning of the retinal pigment epithelium between the macula and the optic disc. The ERG record for two patients revealed reduced amplitude of cone response. No systemic abnormalities were noted in any affected individual. The disease in this family

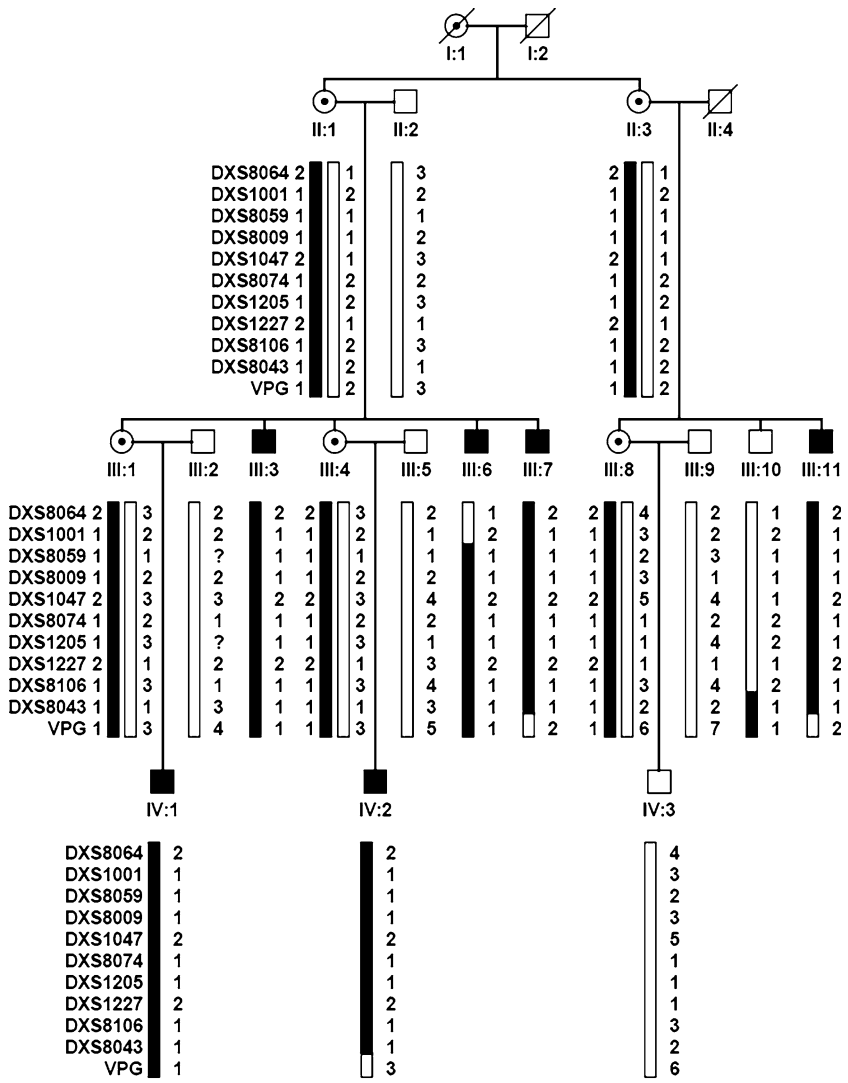


**Fig. 1** Pedigree and haplotype diagram of the family with high myopia. *Blackened bars* indicate disease allele. *Filled squares* represent individuals affected by high myopia. *VPG* represents array patterns of red–green visual pigment genes. *Filled* (*vertical*) *bars* indicate the phased haplotype associated with the disease in II-1 and II-3. The *filled portions* in the descendants indicate the chromosomal regions that are derived from the disease-associate haplotype in their ancestors

**Table 1** Two-point linkage results for markers in the high myopia region at Xq25-q27.2

| Markers | Position | | Lod score at theta = | | | | | | | $Z_{max}$ | $\theta_{max}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | cM | Mb | 0.00 | 0.01 | 0.05 | 0.10 | 0.20 | 0.30 | 0.40 | | |
| DXS8064 | 131.80 | 117.16 | –∞ | 0.75 | 1.25 | 1.31 | 1.10 | 0.73 | 0.31 | 1.31 | 0.09 |
| DXS1001 | 139.40 | 119.72 | –∞ | 0.75 | 1.25 | 1.31 | 1.10 | 0.73 | 0.31 | 1.31 | 0.09 |
| DXS8059 | 141.90 | 122.09 | 0.38 | 0.37 | 0.33 | 0.29 | 0.19 | 0.11 | 0.04 | 0.38 | 0.00 |
| DXS8009 | 148.40 | 126.00 | 0.99 | 0.97 | 0.89 | 0.80 | 0.60 | 0.40 | 0.20 | 0.99 | 0.00 |
| DXS1047 | 150.30 | 128.90 | 2.79 | 2.74 | 2.53 | 2.26 | 1.70 | 1.09 | 0.46 | 2.79 | 0.00 |
| DXS8074 | 152.70 | 133.91 | 2.49 | 2.45 | 2.27 | 2.04 | 1.55 | 1.01 | 0.42 | 2.49 | 0.00 |
| DXS1205 | 163.70 | 140.09 | 2.49 | 2.45 | 2.27 | 2.04 | 1.55 | 1.01 | 0.42 | 2.49 | 0.00 |
| DXS1227 | 164.70 | 140.63 | 2.79 | 2.74 | 2.53 | 2.26 | 1.70 | 1.09 | 0.46 | 2.79 | 0.00 |
| DXS8106 | 173.60 | 142.01 | 2.79 | 2.74 | 2.53 | 2.26 | 1.70 | 1.09 | 0.46 | 2.79 | 0.00 |
| DXS8043 | 176.70 | 143.84 | –∞ | 0.15 | 0.70 | 0.80 | 0.69 | 0.44 | 0.15 | 0.80 | 0.11 |
| VPG | | 153.10 | –∞ | –5.24 | –2.56 | –1.50 | –0.60 | –0.21 | –0.03 | 0.00 | 0.48 |

shares clinical features observed in the family mapped to MYP13, including high myopia, myopic fundus, and abnormal cone response on ERG recordings. Red–green color vision defects were found in III:3, III:6, and IV:1 of the six individuals with high myopia; Ishihara plates screening and heteroduplex-SSCP analysis of exon 5 of red–green visual pigment genes (data not shown) suggested these were deutan-based. Unaffected individual III:10 also had deutan. It is, therefore, obvious the color-vision defects are not associated with high myopia in the family.

On X-chromosome-wide linkage analysis, maximum two-point lod scores of 2.79 were obtained for DXS1047, DXS1227, and DXS8106 (Table 1). Haplotype analysis revealed a conserved haplotype between DXS1047 and DXS8043. This haplotype was present in all the affected individuals and unaffected carriers but not in unaffected males (Fig. 1). An obligate recombinant at DXS1001 in affected individual III:6 set the proximal boundary. Recombination at VPG (red–green visual pigment genes) in affected individuals III:7, III:11, and IV:2 set the telomeric boundary for the linked region. A recombination occurred between DXS8106 and DXS8043 in the closely related normal individual III:10 who carried the partial haplotype seen in affected individuals, suggesting the causative gene is proximal to DXS8043. The linked interval for high myopia in this family is therefore located in the 37.3 cM (24.11 Mb) region at Xq25-q27.2 between DXS1001 and DXS8043.

## Discussion

In this study X-linked recessive high myopia in a Chinese family has been mapped to Xq25-q27.2 between DXS1001 and DXS8043. The maximum lod score over two at theta = 0 in two-point linkage analysis for five neighboring markers established a linkage for high myopia on the X chromosome according to the conventional criteria for X-linked disease (Terwilliger and Ott 1994). Exclusion of other region of the X chromosome and the MYP1 region, a maximum two point lod score of 2.79, and haplotype observation all support a locus for X-linked recessive high myopia in the family.

Two loci for X-linked recessive high myopia, MYP1 and MYP13, have been reported previously. The linkage interval in this study is approximately 15.8 cM (6.03 Mb) away from MYP1, which is located at Xq28 distal to DXS 8103 (Schwartz et al. 1990; Young et al. 2004). The current linkage interval overlaps by approximately 4.80 cM (3.68 Mb) with MYP13, which is located between DXS1210 and DXS8057. The high myopia locus for this family is, therefore, overlapped with MYP13 but outside MYP1. We are not sure whether this study provides additional information to refine MYP13 or whether the results are indicative of a new locus for high myopia. Our results do, however, provide additional evidence that a myopia locus on the long arm of the X chromosome is outside MYP1.

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## References

Anonymous (1989) Standard for clinical electroretinography. International Standardization Committee. Arch Ophthalmol 107:816–819

Guo X, Li S, Jia X, Xiao X, Wang P, Zhang Q (2006) Linkage analysis of two families with X-linked recessive congenital motor nystagmus. J Hum Genet 51:76–80

Naiglin L, Gazagne C, Dallongeville F, Thalamas C, Idder A, Rascol O, Malecaze F, Calvas P (2002) A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. J Med Genet 39:118–124

Paluru P, Ronan SM, Heon E, Devoto M, Wildenberg SC, Scavello G, Holleschau A, Makitie O, Cole WG, King RA, Young TL (2003) New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. Invest Ophthalmol Vis Sci 44:1830–1836

Paluru PC, Nallasamy S, Devoto M, Rappaport EF, Young TL (2005) Identification of a novel locus on 2q for autosomal dominant high-grade myopia. Invest Ophthalmol Vis Sci 46:2300–2307

Pararajasegaram R (1999) VISION 2020-the right to sight: from strategies to action. Am J Ophthalmol 128:359–360

Schwartz M, Haim M, Skarsholm D (1990) X-linked myopia: Bornholm eye disease. Linkage to DNA markers on the distal part of Xq. Clin Genet 38:281–286

Terwilliger JD, Ott J (1994) Handbook of human genetic linkage. John Hopkins University Press, Baltimore

Young TL, Ronan SM, Alvear AB, Wildenberg SC, Oetting WS, Atwood LD, Wilkin DJ, King RA (1998a) A second locus for familial high myopia maps to chromosome 12q. Am J Hum Genet 63:1419–1424

Young TL, Ronan SM, Drahozal LA, Wildenberg SC, Alvear AB, Oetting WS, Atwood LD, Wilkin DJ, King RA (1998b) Evidence that a locus for familial high myopia maps to chromosome 18p. Am J Hum Genet 63:109–119

Young TL, Deeb SS, Ronan SM, Dewan AT, Alvear AB, Scavello GS, Paluru PC, Brott MS, Hayashi T, Holleschau AM, Benegas N, Schwartz M, Atwood LD, Oetting WS, Rosenberg T, Motulsky AG, King RA (2004) X-linked high myopia associated with cone dysfunction. Arch Ophthalmol 122:897–908

Zhang Q, Minoda K (1996) Detection of congenital color vision defects using heteroduplex-SSCP analysis. Jpn J Ophthalmol 40:79–85

Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF (2005) A new locus for autosomal dominant high myopia maps to 4q22-q27 between D4S1578 and D4S1612. Mol Vis 11:554–560

Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF (2006) Novel locus for X linked recessive high myopia maps to Xq23-q25 but outside MYP1. J Med Genet 43:e20