ELECTRONIC LETTER

Novel locus for X linked recessive high myopia maps to Xq23–q25 but outside MYP1

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Background: High myopia is a common genetic variation in most cases, affecting 1–2% of people, and is the fourth most common disorder causing blindness worldwide. Six autosomal dominant loci and one X-linked recessive locus have been reported, but no genes responsible for high myopia have been identified.

Objective: To report a Chinese family in which six males presented with high myopia consistent with an X linked recessive trait.

Results: Affected individuals shared three common features: high myopia, reduced visual acuity, and fundal changes of high myopia. Protan and deutan were observed in the family, but they did not co-segregate with the high myopia phenotype. X-chromosome-wide linkage analysis mapped the high myopia locus to a 25 cM (14.9 Mb) region on Xq23–q25 between DXS1210 and DXS8057, with maximum two point lod scores at $\theta = 0$ of 2.75 and 2.29 for DXS1001 and DXS8059, respectively.

Conclusions: This new myopia locus is outside the linked region of the first high myopia locus (MYP1). Refinement of the linkage region with additional families and screening candidate genes for mutation may lead to the identification of the defect gene.

Myopia is the most common ocular health problem, affecting an average of about 30% (3% to 84%) of people throughout the world, usually for most of a person's life.[1–6] The cost involved in correction of this problem is enormous,[4 7] accounting for about one fourth of the entire expenditure in ophthalmology and optometry.

High myopia, the fourth most common cause of blindness, is an extreme form of myopia associated with retinal detachment and macular degeneration, occurring in 1–2% of the general population.[8–12] It may be inherited as an autosomal dominant, autosomal recessive, X linked recessive, or complex trait. The genes responsible for high myopia have not been identified, although several chromosomal loci have been suggested.[9–11 13–17] Most of these loci have not been confirmed by independent study, suggesting that the identified loci may be responsible for only a small portion of high myopia.[18] A small fraction of high myopia is associated with other ocular or systemic diseases as part of a syndrome.[19–23] The first locus (MYP1) for high myopia was mapped to Xq28 in 1990 but its genetic basis remains unknown.[13 17]

A four generation Chinese family with X linked recessive high myopia was collected in order to map the genetic locus as an initial step towards identifying the genetic cause of this condition. An X-chromosome-wide linkage study was undertaken and the myopia in the family was mapped to a novel locus on Xq23–q25, which is outside the linkage region of MYP1.

METHODS

Family and clinical data

A Chinese family of Han ethnicity with X linked recessive high myopia was identified in a small town in southeast China. This family has six affected individuals in four generations. Sixteen individuals, including five affected and 11 unaffected, participated in the study. Informed consent conforming to the tenets of the Declaration of Helsinki and following the Guidance of Sample Collection of Human Genetic Diseases (863-Plan) by the Ministry of Public Health of China was obtained from the participating individuals before the study. Medical and ophthalmic histories were obtained, and ophthalmological examination was carried out (by XG). Refractive error was measured by retinoscopy. A subject was considered to have high myopia if they met the following criteria:

- the myopia was noted before school age;
- there was bilateral cycloplegic refraction of −6.00 D or lower (spherical equivalent) in individuals <30 years of age, or manifest refraction of −6.00 D or lower (spherical equivalent) in individuals 30 years or more of age;
- other known ocular or systemic diseases were excluded.

Electroretinogram (ERG) responses were recorded in the proband consistent with ISCEV standards.[24] Colour vision was evaluated using an Ishihara plate and classified by analysing exon 5 of red-green visual pigment genes, as previously described.[25 26]

Genotyping and linkage analysis

Genomic DNA was prepared from venous blood. An X-chromosome-wide linkage scan was carried out as previous described, except that only microsatellite markers for the X chromosome were analysed.[15] High myopia in the family was analysed as an X linked recessive trait with full penetrance and a disease allele frequency of 0.0001. Haplotypes were generated using the Cyrillic 2.1 program and confirmed by inspection. Equal marker allele frequencies were arbitrarily assumed for the initial scan and were calculated from 15 unrelated unaffected individuals for markers in the linked region.

RESULTS

The myopia in five affected individuals ranged from −6.00 D to −20.00 D. Refractive error for unaffected siblings, offspring, and individuals marrying into the family was between −3.00 D and +2.00 D. All affected individuals developed myopia before school age and the best corrected visual acuity was rather poor, between 0.15 and 0.5 (table 1). Progression of myopia was slow except in case 19. No patient had night

Abbreviations: AMD, age related macular degeneration; ERG, electroretinogram; ISCEV, International Society for Clinical Electrophysiology of Vision

Table 1 Clinical data on the family members participating in the study

ID	Sex	Age (y)	Age at first symptom	Visual acuity Unaided (corrected) R eye	Visual acuity Unaided (corrected) L eye	Refraction R eye	Refraction L eye	Others	Nystagmus
3	M	43		1.0	1.0	0	0	Protan	No
4	F	60		0.5	0.2	Hyperopia and astigmatism		No	No
6	F	49		1.0	0.8	0	0	No	No
10	F	68	15 y	(0.5)	(0.5)	−3.00 D	−3.00 D	No	No
12	M	35	<7 y	(0.5)	(0.5)	−6.00 D	−7.00 D	Deutan	No
14	M	32	<7 y	(0.15)	(0.3)	−8.00 D	−8.00 D	Deutan	Yes
15	F	33		1.0	1.0	0	0	No	No
17	F	36		1.2	1.0	0	0	No	No
18	M	36		1.2	1.2	0	0	No	No
19	M	29	<7 y	(0.15)	(0.15)	−22.00 D	−23.00 D	Protan	No
25	M	7	<5 y	(0.4)	(0.4)	−6.00 D	−7.00 D	No	No
35	F	72		0.3	0.3	+2.00 D	+2.00 D	AMD	No
37	M	70		0.2	0.08	−1.00 DS to 1.00 DC	−2.00 DS to 1.5 DC	No	Yes
42	M	46		0.8	0.8	−1.00 DS to 1.5 DC	−1.00 DS to 1.5 DC	No	No
43	M	40		1.0	0.8	0	−0.50 DS	No	No
51	M	19	<7 y	(0.4)	(0.4)	−5.50 DS to 2.00 DC	−6.00 DS to 1.50 DC	No	No

AMD, age related macular degeneration; D, dioptre; DC, dioptres cylinder; DS, dioptres sphere; F, female; L, left; M, male; R, right; y, years.

blindness or photophobia. One affected individual (No 14) and one unaffected individual (No 37) had nystagmus. Age related macular degeneration (AMD) was observed in case 35.

Red-green colour vision defects were found in three of the five affected individuals (Nos 12, 14, and 19) and were identified as having patterns of protan in individual 19 and deutan in individuals 12 and 14, based on Ishihara plate screening and heteroduplex-SSCP analysis of the exon 5 of red-green visual pigment genes (data supplied as supplemental material and can be seen on the journal website: www.jmedgenet.com/supplemental). Unaffected individual No 3 also had protan. It is thus obvious that the colour vision defects are not associated with high myopia in this family.

Ophthalmological examination excluded ocular diseases known to be associated with myopia. All affected individuals had a temporal crescent of the optic disc, thinning of the retinal pigment epithelium (''tigroid'' appearance) between the fovea and the optic disc, and posterior extension of central macular region, as demonstrated in the proband (fig 1). Ocular A-scan of the proband at age seven years recorded an axial length of 25.55 mm for the right eye and 25.90 mm for the left. Keratometry at the same time gave 42.00/40.00D for the right eye and 42.50/40.50D for the left. ERG in the proband showed severely reduced amplitude of the cone response. The implicit times of the rod response were delayed (fig 2). No systemic abnormalities were noted in any affected individual. Female carriers have normal visual acuity, normal fundal appearances, and normal responses on ERG recording (figs 1 and 2), except that reduced visual acuity has been recorded in individuals 10 and 35. Individual 10 had a normal fundal appearance and the reason for her reduced visual acuity is unknown. AMD may be contributing to the reduced visual acuity as she says she had better vision when she was young.

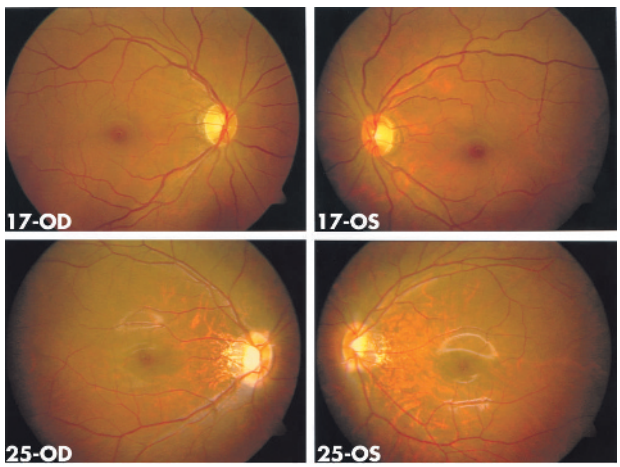

Figure 1 Fundus photographs of individuals 17 (carrier, top) and 25 (affected, bottom). The temporal crescent of the optic disc and thinning of the retinal pigment epithelium between the macula and optic disc are seen in individual 25 but not in the normal fundus of individual 17.

The affected Chinese individuals share three common phenotypes: high myopia; reduced visual acuity which is stationary and could not be corrected; and typical high myopic fundal changes.

Upon linkage analysis of the X chromosome, maximum two point lod scores of 2.75 and 2.29 were obtained for DXS1001 and DXS8059 (table 2). Haplotype analysis showed a conserved haplotype between DXS1059 and DXS8059. This haplotype is present in all affected individuals as well as in unaffected carriers, but not in unaffected males (fig 3). An obligate recombinant at DXS1210 in affected individual 25 and confirmed in carrier individual 17 sets the proximal boundary. Recombination at DXS8057 in affected individual 51 and further recombination at DXS8106 in affected individual 19 sets the telomeric boundary for the linked region. Thus the linked interval for high myopia in this family is located in the 25 cM (14.9 Mb) region at Xq23–q25 between DXS1210 and DXS 8057.

DISCUSSION

We report X linked recessive high myopia with reduced visual acuity in a Chinese family. The lack of macular degeneration seen in other types of hereditary retinopathy, the stationary reduction in visual acuity in all the affected individuals, and the reduced ERG cone response shown in the proband all suggest cone dysfunction in the affected individuals. Such phenotypes were also found in a further four large Chinese families with X linked recessive high myopia (manuscript in preparation). In this study, the high myopia is assigned to a new locus on chromosome Xq23–q25 between DXS1210 and DXS8057. Exclusion of other regions in the X chromosome including the MYP1 region, a maximum two point lod score of 2.75, and haplotype observation all support a new locus for

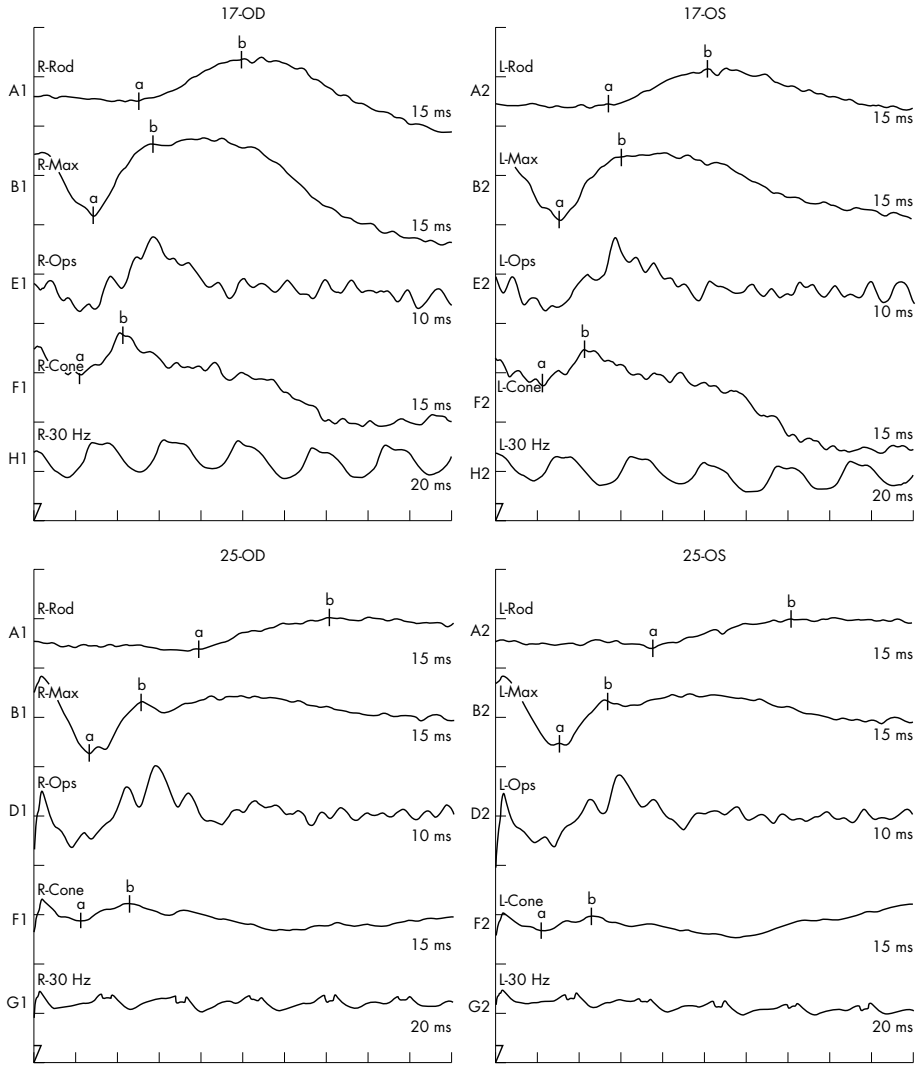

Figure 2 Severely reduced amplitude of the cone response and delayed implicit time of the rod response in the electroretinogram (ERG) recording of individual 25. His mother (individual 17) has normal cone-rod response in the ERG recording.

X linked recessive high myopia in this family. There are about 101 genes in the linked interval. Possible candidate genes include, but are not limited to, GUCY2F, GLUD2, GRIA3, BIRC4, STAG2, and LRCH2.

The first locus (MYP1) for high myopia,[13 17] which was excluded in this study by linkage and haplotype analysis, is at least 16.66 Mb (42 cM) away from the telomeric boundary of the new locus. Individuals from both branches of the current family show obligate recombinations with this region. MYP1 was mapped to Xq28 by linkage analysis of a large Danish family with Bornholm eye disease, using three markers. Exclusion of other regions of the X chromosome has not been carried out and the diagnostic criteria were not meet by all affected individuals in the linkage analysis in that family.[13 27] Another family with X linked high myopia associated with cone dysfunction, of Danish origin, was mapped to Xq27.3–q28.[17] The disease in the Chinese family shares some features observed in those two families mapped to MYP1, including high myopia, impaired visual acuity, a myopic fundus, and abnormal cone responses on ERG recordings. Colour vision defects are present in all affected members in the previous two families mapped to MYP1 but in only three of the five affected individuals (two with deutan and one with protan) in the Chinese families, although variations in the visual pigment genes was not responsible for myopia.[17] Apart from high myopia, common myopia has been shown to be linked to Xp,[28 29] which is away from the novel locus identified in the Chinese family. Ocular refraction has been shown to have sex linked effect but its linked region on the X chromosome has not been identified.[30] Different prevalences of refractive errors have been observed between males and females.[31] All these indicate the importance of X linked genes in myopia development.

In addition, X linked high myopia has been well documented in association with congenital stationary night blindness (CSNB1/NYX)[22] and retinitis pigmentosa (RP2).[23] Mild to high myopia has been observed in other X linked ocular diseases includes cone-rod dystrophy[32–34] and Aland eye disease.[35] The loci for these myopia associated syndromes are located outside the linked interval of the high myopia in the Chinese family.

In summary, a novel locus for X linked recessive high myopia in a Chinese family is mapped to Xq23–q25 with the highest lod score being 2.75 for DXS1001 at $\theta = 0$. This locus is at least 16.66 Mb away from MYP1. Refinement of the linkage region with additional families and screening candidate genes for mutation may lead to the identification of the defect gene.

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Table 2 Two point linkage results between microsatellite markers of the X chromosome and high myopia in the Chinese family

	Position		Lod score at θ =						
Markers	CM	Mb	0	0.01	0.05	0.1	0.2	0.3	0.4
DXS1060	10.10	5.27	−∞	−7.31	−3.91	−2.51	−1.24	−0.61	−0.23
DXS8051	15.70	9.31	−∞	−4.27	−2.16	−1.28	−0.50	−0.17	−0.03
DXS987	25.50	14.47	−∞	−3.47	−1.49	−0.74	−0.16	0.03	0.05
DXS1226	36.80	?	−∞	−1.92	−0.65	−0.20	0.08	0.12	0.08
DXS1214	46.20	31.02	−∞	−5.43	−2.71	−1.60	−0.63	−0.20	−0.01
DXS1068	56.20	38.66	−∞	−4.35	−2.28	−1.43	−0.66	−0.29	−0.10
DXS993	66.10	40.90	−∞	−0.50	0.20	0.45	0.56	0.47	0.28
DXS8080	71.60	44.00	−∞	−1.65	−0.88	−0.54	−0.22	−0.08	−0.02
DXS991	86.90	55.40	−∞	1.11	1.62	1.67	1.44	1.04	0.56
DXS1213	87.40	65.05	−∞	−0.77	−0.05	0.22	0.38	0.35	0.22
DXS8052	94.20	69.60	−∞	0.47	1.01	1.11	0.99	0.71	0.36
DXS986	95.90	79.19	−∞	−1.17	0.11	0.54	0.77	0.69	0.42
DXS990	104.90	92.81	−∞	−1.17	0.11	0.54	0.77	0.69	0.42
DXS1106	115.10	102.54	−∞	−0.77	−0.11	0.12	0.26	0.24	0.14
DXS1210	119.20	108.40	−∞	−2.17	−0.83	−0.32	0.07	0.16	0.13
DXS1059	121.00	111.13	0.57	0.56	0.51	0.44	0.32	0.20	0.09
DXS8088	122.80	113.16	0.50	0.49	0.45	0.41	0.31	0.20	0.09
DXS8064	131.80	117.05	0.61	0.60	0.56	0.51	0.41	0.29	0.16
DXS1001	139.40	119.62	2.75	2.70	2.51	2.27	1.75	1.20	0.61
DXS8059	141.90	121.99	2.29	2.25	2.10	1.90	1.47	1.01	0.52
DXS8057	144.20	123.30	−∞	−0.55	0.15	0.40	0.51	0.42	0.23
DXS8009	148.40	125.90	−∞	−1.45	−0.19	0.23	0.45	0.40	0.23
DXS1047	150.30	128.80	−∞	−1.63	−0.37	0.05	0.29	0.27	0.16
DXS8074	152.70	133.81	−∞	−2.34	−1.09	−0.66	−0.38	−0.27	−0.15
DXS1062	153.70	137.03	−∞	−2.15	−0.81	−0.30	0.08	0.17	0.13
DXS1205	163.70	139.99	−∞	0.52	1.07	1.17	1.04	0.76	0.40
DXS1227	164.70	140.53	−∞	−0.57	0.01	0.16	0.15	0.04	−0.02
DXS8106	173.60	141.91	−∞	−2.26	−1.01	−0.58	−0.24	−0.05	0.04
DXS8043	176.70	143.73	−∞	−3.73	−1.70	−0.90	−0.22	0.04	0.09
DXS8091	186.30	147.31	−∞	−4.68	−2.60	−1.74	−0.94	−0.53	−0.24
DXS8069	190.40	149.31	−∞	−2.91	−0.96	−0.26	0.21	0.29	0.19
DXS1073	196.50	153.39	−∞	−3.46	−1.45	−0.67	−0.03	0.17	0.17

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Supplementary data can be viewed on the journal website (www.jmedgenet.com/supplemental)

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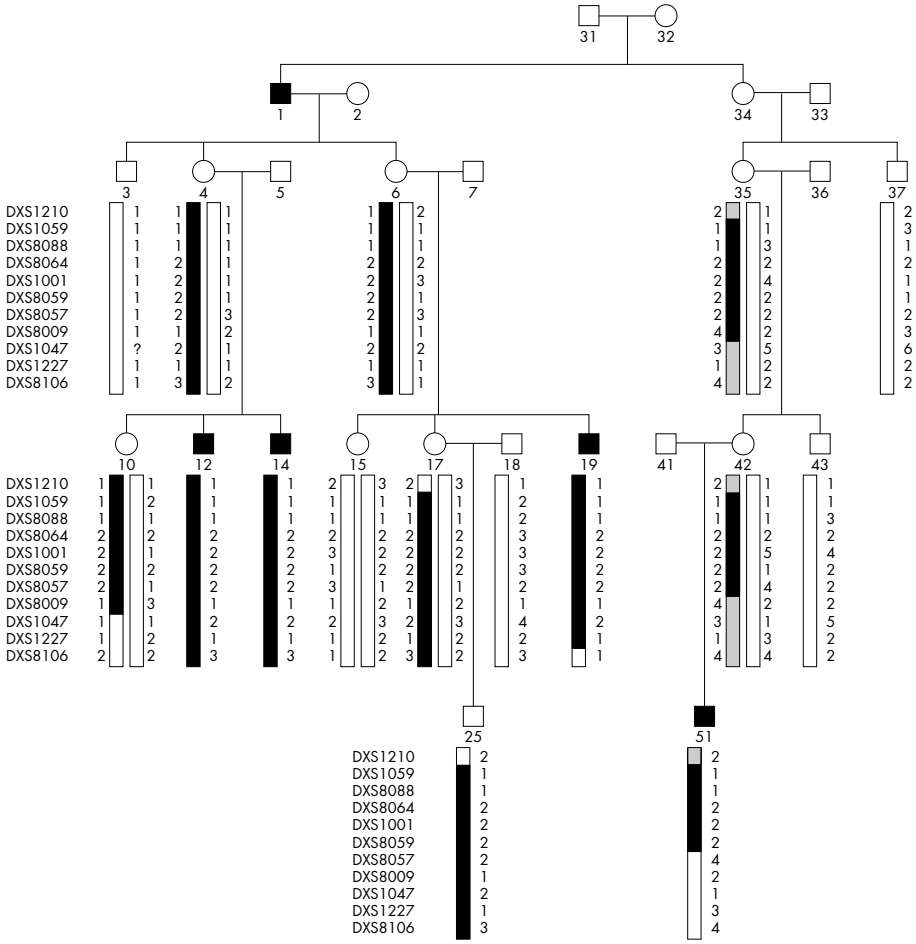

Figure 3 Pedigree and haplotype diagram of the family with X linked high myopia. Blackened bars indicate disease alleles. Filled squares represent individuals affected with high myopia.

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