

doi: 10.3325/cmj.2009.50.17

Common Variant in Myocilin Gene Is Associated with High Myopia in Isolated Population of Korčula Island, Croatia

Aim To study the association between genetic variants in myocilin and collagen type I alpha 1 genes and high myopia in an isolated island population.

Methods A total of 944 examinees from the genetic epidemiology study conducted on the island of Korčula, Croatia, were included in the study. We selected 2 short nucleotide polymorphisms (SNP) available in our genome-wide scan set of SNPs that were previously associated with high myopia and used them to replicate previous claims of possible association.

Results Nineteen cases of high myopia, defined as the refraction of ≤ -6.00 diopters, were identified and included in the analysis. We showed that rs2075555 in the *COL1A1* gene was not associated with high myopia. In contrast, rs2421853 in the myocilin gene was significantly associated in both bivariate ($P=0.006$) and age- and sex-adjusted analysis ($P=0.049$).

Conclusion Myocilin seems to be a very strong candidate for explaining some of the pathophysiological pathways leading to the development of both glaucoma and high myopia. As our finding was obtained in a relatively underpowered sample, further research and replication of these results is needed.

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Received: December 16, 2008

Accepted: January 23, 2009

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Individual variation in eye morphometry traits is responsible for numerous ocular conditions, ranging from mild refractive errors to potentially vision-threatening diseases such as macular degeneration and glaucoma (1,2). It is estimated that a half of the United States population aged 20 and older is affected by clinically important refractive conditions, myopia or hyperopia (3). Among ocular morphometric traits, axial length is considered to be the most important determinant of refraction (4).

Both environmental and genetic factors have been shown to affect the development of refractive errors. Sudden increase in the prevalence of myopia, especially in Asian countries, where up to 90% of young adults are affected, suggests possible environmental or behavioral causes (5,6). However, twin studies demonstrated genetic effect and showed that heritability of refractive error and axial length is high, reaching up to 94% (7,8).

High myopia, defined as refraction of ≤ -6.00 diopters (9), has been associated with various adverse effects and is a frequent cause of legal blindness, especially in younger patients, due to macular degeneration, glaucoma, or retinal detachment (1,2,10,11). This creates a considerable socioeconomic burden for the affected individuals and their families (12). Several possible variants determining high myopia have been discovered, with rather variable results among different populations (13-15). One of such genes is myocilin gene, which was already associated with both juvenile open angle glaucoma and primary open angle glaucoma (16-18). Another is the collagen type I alpha 1 (COL1A1) gene on the chromosome 17q22-q23.3, which has been found to be implicated in pathogenesis of high myopia in the Japanese population (19).

Axial length is the most important determinant of refractive error, which has been associated with chromosome 2p24 in the isolated Sardinian population (20). Suggestive linkage of axial length to chromosome 5q has also been described (21). Both of these studies used genome-wide scans based on very scarcely distributed microsatellite markers. On the other hand, more recent genome-wide association studies have used SNPs as a tool for gene mapping, allowing much denser genome-wide scans and finer mapping (22).

The genetic epidemiology research program in Croatian island isolates began in 1999 (23,24), was expanded to study human genetic variation and the effects of isolation and inbreeding (25-33), and later broadened its

focus to include diseases and gene mapping studies (34-41). By now, the research project has included more than 3000 examinees from isolated populations and aims to eventually reach 10001 of them.

The aim of this study was to investigate the reported association between two genomic SNP markers, representing genetic variants in the *COL1A1* and myocilin gene, and high myopia, using the genetic epidemiology resource from the isolated population of the Island of Korčula, Croatia.

MATERIALS AND METHODS

This study included adult inhabitants of the Korčula Island, Croatia. The participants were recruited from general practitioners' records. Also, we tried to increase the number of participants by making invitations through radio announcements, personal contacts, postal service, and e-mail. All examinees were aged 18 or more and had signed an informed consent. The study was approved by the Ethical Committee of the School of Medicine, University of Zagreb, Croatia.

Refraction data were obtained by using automated keratorefractometer (Nidek ARK-30, Nidek S.A., Créteil, France), with examinees in a supine position. After keratorefractometry, one drop of 0.5% tetracaine hydrochloride (Tetrakain, Pliva, Zagreb, Croatia) was instilled in each eye to anesthetize corneal surface. Axial length was measured by A-scan ultrasound (Nidek Echoscans US-1800, Nidek S.A.). High myopia was defined as the refraction of ≤ -6.00 diopters (using spherical equivalent, defined as the sum of spherical power and half of cylindrical refraction power, where values between -6 and -17 were classified as high myopia). Examinees with the required refraction in either eye were considered to have high myopia. History of cataract surgery ($n=34$), retinal detachment ($n=7$), or other ocular conditions influencing refraction ($n=11$) were the exclusion criteria. A total of 969 examinees were recruited in the field work. All examinees provided a sample of blood, which was centrifuged on the spot and leukocytes were isolated and used for the DNA extraction. DNA extraction was performed using Qiagen kit (Tepnel, Manchester, UK). A total of 944 examinees were genotyped using Sentrix® HumanHap Genotyping BeadChip, version 2 (Illumina Inc, San Diego, CA, USA).

The data are presented as percentages for categorical variables and medians with interquartile ranges for numerical variables. Categorical data were analyzed using Fisher ex-

TABLE 1. Descriptive statistics for right and left eye spherical and cylindrical power in the Korčula island sample

Parameter	Sex differences (median, interquartile range)		Correlation with age		<i>P</i> [†]
	Men	Women	<i>P</i> [*]	Correlation coefficient	
Right eye spherical power	-0.37 (1.49)	-0.12 (1.62)	0.025	0.33	<0.001
Right eye cylindrical power	0.37 (0.87)	0.37 (0.63)	0.502	0.25	<0.001
Left eye spherical power	-0.25 (1.81)	-0.12 (1.75)	0.489	0.35	<0.001
Left eye cylindrical power	0.37 (0.87)	0.37 (0.63)	0.852	0.22	<0.001

*Mann-Whitney test.

†Spearman rank test.

act test. Two groups of numerical data were analyzed with Mann-Whitney test, while Spearman rank test was used in the correlation analysis. Also, multivariate analysis (logistic regression) was performed with age and sex as covariates. All analyses were performed in the SPSS, version 13 (SPSS Inc, Chicago, IL, USA), with $P < 0.05$ as the level of statistical significance.

RESULTS

In our participants, median values of right and left spherical and cylindrical power showed certain level of sex effect (right eye spherical power) and a correlation with age (Table 1). Among 944 examinees, 19 had the diagnosis of high myopia. There were 4 men (21%) and 15 women (79%) with high myopia, but this difference was not significant ($P = 0.173$, Fisher exact test).

The rs2421853 in myocilin gene was significantly associated with high myopia in the bivariate analysis, while rs2075555 in the *COL1A1* gene was not (Table 2). Finally, the first SNP maintained significance in the logistic regression model, after adjusting for the effects of age and sex (Table 3). Within this SNP, AA increased the risk of having high myopia almost five times, compared with AG and GG, which had a protective effect (Table 3). This SNP explained a total of 2.5% of variance (Nagelkerke $R^2 = 0.025$).

DISCUSSION

This study identified a common SNP in myocilin gene as the genetic variant that confers strong risk of high myopia in the isolated population sample of the island of Korčula. Previous studies have so far identified a number of potential candidate genes which determine high myopia, including *COL1A1* (19), *COL2A1* (42), *lumican* (43), *EGR1* (44), and myocilin (18). We selected two SNPs available in our

TABLE 2. Sample breakdown according to the short nucleotide polymorphisms (SNP) and presence or the absence of high myopia

SNP	No. (%) of subjects			<i>P</i> [*]
	without high myopia	with high myopia	total	
rs2421853				
AA	44 (5.2)	3 (19)	47 (5.5)	0.006
AG	296 (35)	3 (19)	299 (35)	
GG	504 (60)	10 (63)	514 (60)	
total	844 (100)	16 (100)	860 (100)	
rs2075555				
AA	19 (2.4)	0 (0)	19 (2.3)	0.137
AG	210 (26)	5 (29)	215 (27)	
GG	565 (71)	12 (71)	577 (71)	
total	794 (100)	17 (100)	811 (100)	

*Fisher exact test.

TABLE 3. The age- and sex-adjusted effects of the short nucleotide polymorphisms (SNP) rs2421853 (myocilin gene) on the high myopia (logistic regression)

Variable	<i>P</i>	Odds ratio
		(95% confidence interval)
Age	0.443	0.99 (0.95-1.02)
Sex		
men (Ref.)		1.00
women	0.38	1.68 (0.53-5.33)
rs2421853		
AA (Ref.)	0.049	1.00
AG	0.017	0.14 (0.03-0.70)
GG	0.050	0.26 (0.07-0.99)

genome-wide scan set of SNPs that were previously associated with high myopia and used them in this analysis to replicate previous claims of possible association. We replicated the results for myocilin variant, but not for *COL1A1* variant.

The myocilin gene, located on chromosome 1q24-q25, encodes a myocilin protein, which has been associated with cytoskeletal function. It is expressed in many tissues, most notably in the ciliary body, iris, trabecular meshwork, sclera, choroid, and retina (45). Mutations in the myocilin gene were found in patients with open angle glaucoma, but also in patients with other types of glaucoma, such as normal tension, pigmentary, and exfoliation glaucoma (46). Myopia is a known risk factor for open angle glaucoma and myopic eyes frequently exhibit higher intraocular pressure in comparison with emmetropic eyes (47-51). Thus, our study showed that variants in myocilin gene may be one of the common etiological factors linking the high myopia and open angle glaucoma.

Tang et al showed that myocilin polymorphisms have been associated with high myopia in the Chinese population (18). Association was shown for SNP rs2421853 and SNP rs235858, with the latter showing higher degree of significance. Linkage studies have connected chromosomes 2q, 3q26, 4q, 7q, 10q, 12q, 17q, 18p, and 22q and high myopia (50-58). However, all these reports need to be taken with a great deal of caution because it is likely that most historic genome-wide scans based on STR markers and linkage approach were underpowered to detect true effects and also very prone to false-positive findings. Even though several studies analyzed isolated populations, none of them has shown a linkage to myocilin (54,58). In our study population, we replicated the effect of SNP rs2421853, but not of the SNP rs235858. Despite the fact that the study by Tang et al was a family-based association study with 557 members from 162 nuclear families, with at least one offspring with high myopia and that our study was population-based, we were able to demonstrate the value of population isolates in detecting loci for complex diseases. Furthermore, the results of this study show relatively high percent of variance explained (2.5%), making this gene an even more likely candidate for further functional research and sequencing.

The limitations of this study include the small number of cases (only 19). Also, we were able to study only two implicated SNPs available in our genome-wide scan, although the trait we wanted to explain was highly complex (59). One of the best strategies to further investigate this finding would be to substantially increase statistical power, either by increasing the number of examinees (what would not be very feasible in the population genetic cross-sectional approach) or by performing case-control study of high myopia. The best approach would be to combine the results from several studies and perform a large-

scale meta-analysis of published and unpublished studies on both the genetic markers and ophthalmological measurements. Approaches such as Mendelian randomization (60) could further reduce the chances of spurious associations. However, the finding of a biologically highly plausible candidate gene in the investigated population is encouraging and warrants further research on the role of myocillin in high myopia etiology.

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