Meta Gene 2 (2014) 164–175

Contents lists available at ScienceDirect

Meta Gene

Genetic analysis of axial length genes in high grade myopia from Indian population ☆

Ferdinamarie Sharmila [a,b], Abinayapriya [c], Karthikeyan Ramprabhu [a], Govindasamy Kumaramanickavel [a], R.R.Sudhir [d], Sarangapani Sripriya [a,*]

[a] SN ONGC, Department of Genetics and Molecular Biology, Vision Research Foundation, India
[b] Birla Institute of Technology & Science (BITS), Pilani, 333 031 Rajasthan, India
[c] Medical Research Foundation, Sankara Nethralaya, Chennai, India
[d] Preventive Ophthalmology Department, Sankara Nethralaya, Chennai, India

ARTICLE INFO

Article history:
Received 6 August 2013
Revised 9 January 2014
Accepted 9 January 2014
Available online 15 February 2014

Keywords:
Myopia
MFRP
VSX2
Axial length
Quantitative trait

ABSTRACT

Purpose: To study the putative association of Membrane frizzled related protein (*MFRP*) and Visual system homeobox protein (*VSX2*) gene variants with axial length (AL) in myopia.

Method: A total of 189 samples with (N = 98) and without (N = 91) myopia were genotyped for the *MRFP* and *VSX2* variations in ABI Prism 3100 *AVANT* genetic analyzer. Genotype/haplotype analysis was performed using PLINK, Haploview and THESIAS softwares.

Results: Fifteen variations were observed in the *MFRP* gene of which, rs36015759 (c.492C > T, T164T) in exon 5 was distributed at a high frequency in the controls and significantly associated with a low risk for myopia ($P = 4.10 * e^{-07}$ OR <1.0). An increased frequency for the coding haplotype block [CG**T**CGG] harboring rs36015759 was observed in controls (31%) than cases (8%) that also correlated with a decreased mean AL (−1.35085; $P = 0.000444$) by THESIAS analysis. The 'T' allele of rs36015759 was predicted to abolish the binding site for splicing enhancer (SRp40) by FASTSNP analysis.

Conclusion: Myopia is a complex disorder influenced by genetic and environmental factors. Our work shows evidence of association of a specific *MFRP* haplotype which was more prevalent in controls with decreased AL. However, replication and functional studies are warranted to confirm these findings.

* Corresponding author at: SN ONGC Department of Genetics & Molecular Biology, KNBIRVO Block, Vision Research Foundation, 18/41, College Road, Chennai 600 006, India. Tel.: +91 44 42271807, fax: +91 44 28254180.
E-mail addresses: vatsanpriya@gmail.com, drss@snmail.org (S. Sripriya).

http://dx.doi.org/10.1016/j.mgene.2014.01.004
2214-5400/

Introduction

Myopia or nearsightedness is one of the most common human eye disorders with significant global public health concern. It is most prevalent in Taiwan, Japan, China, Korea (east Asia), and Singapore (south east Asia) affecting ~60–80% of young adults (Hsu et al., 2008; Kim et al., 2013a; Lam et al., 2012; Pan et al., 2013; Sawada et al., 2008; Yao et al., 2013). Long term myopia leads to irreversible eye problems which includes chorioretinal degeneration, retinal detachment, lattice degeneration (Asaminew et al., 2013; Koh et al., 2013), glaucoma (Detry-Morel, 2011) etc. and hence poses a serious socio-economic problem. The disease also exhibits an increased progression rate in females when compared to males (Donovan et al., 2012), and follows a complex inheritance pattern with a relative risk of 5 to 20 and 1.5 to 3 for high and low myopia respectively (Farbrother et al., 2004; Guggenheim et al., 2000) in the siblings of a myopic patient. In addition to genetic etiology, various environmental factors, that include near work, education levels (urban compared to rural location) and time spent outdoors have been shown to influence the development of myopic changes; however, the direct role of factors such as near work still remains controversial (Flitcroft, 2012; Jones et al., 2007; Rose et al., 2008).

Family based linkage studies have identified 23 loci till date (Wojciechowski, 2011) most of which have been replicated. Genome wide association/meta analyses (Kiefer et al., 2013; Verhoeven et al., 2013) have associated several loci that include genes involved in neurotransmission (*GRIA4*), ion transport (*KCNQ5*), retinoic acid metabolism (*RDH5*), extracellular matrix remodeling (*LAMA2* and *BMP2*), eye development (*SIX6* and *PRSS56*) and others. In addition to this single nucleotide polymorphisms (SNPs) in candidate genes like *TGFβ* (Ahmed et al., 2013), insulin like growth factor I (Yoshida et al., 2013), *COL1A1* (Zhang et al., 2011), early growth response factor 1(Schippert et al., 2007), *PAX6* (Miyake et al., 2012), matrix metalloproteinase genes (Wojciechowski et al., 2013), hepatocyte growth factor (Chen et al., 2012), *MFRP* (Metlapally et al., 2008), *VSX2* (Aung et al., 2008) etc. have been studied for association with myopia in different populations. Studies pertaining to genetics of myopia from Indian subcontinent have been minimal which includes few candidate gene studies (*TGFβ* (Rasool et al., 2013), *Fok1* (Annamaneni et al., 2011)), linkage studies (Ratnamala et al., 2011), etc.

In this scenario the newer trend of mapping quantitative traits (QT) rather than the disease itself proves to be a better approach for complex disorders such as myopia. The QT/endophenotypes of myopia include axial length (AL) (Cheng et al., 2013), refractive error (Klein et al., 2011), corneal curvature (CC) (Guggenheim et al., 2013), etc. and all these QTs have been studied for their heritability and their contribution to emmetropisation (Chen et al., 2011; Dirani et al., 2006). Among these, AL has been shown as an attractive endophenotype when compared to cornea and crystalline lens (Mutti et al., 2005). AL alone accounts for more than 40% of variation in refractive errors (Cheng et al., 2013; Ip et al., 2007; Pan et al., 2011) and exhibits high heritability factor than that for refraction (Kim et al., 2013b; Klein et al., 2009). The genes implicated with other endophenotypes like CC though important, are also associated with AL. Genetic studies have mapped various chromosomal loci for AL across different populations that include chromosomes 2p24 (Biino et al., 2005), 5q, 12q21 (MYP3), 4q12 (MYP9) (Zhu et al., 2008) and 1q41 (Fan et al., 2012).

So the present study was undertaken as a QTL approach to check for the association of two ocular development genes *MFRP* and *VSX2* with AL in a disease scenario such as myopia where there is improper scaling. Sundin et al. (2008) proposed that *MFRP* had a role in regulation of ocular growth but not critical for retinal function and studies by Aung et al. (2008) and Metlapally et al. (2008) have shown their candidature as AL genes in POAG and myopic cases.

Materials and methods

Clinical examination

The study was approved by the institutional ethics board, adhered to the guidelines in the Declaration of Helsinki and was conducted at the Vision Research Foundation, Sankara Nethralaya, India. Cases were defined with a refractive error worse than −6.00D (N = 98) and controls with +0.50 to −0.50D (N = 91) in the least myopic eye. Subjects with other ocular diseases that predispose/associated with myopia were excluded from the study. Informed consent was obtained from the patients and controls for the research