New ZNF644 mutations identified in patients with high myopia

Xinyaing Xiang,1,4 Tianyun Wang,1 Ping Tong,2 Yunping Li,2 Hui Guo,1,4 Anran Wan,1 Lu Xia,1 Yanling Liu,1 Ying Li,1 Qi Tian,1 Lu Shen,1 Xinzhong Cai,1 Lei Tian,2 Xuemin Jin,3 Kun Xia,1,4,5 Zhengmao Hu1,4

(The first two authors contributed equally to this work.)

1The State Key Laboratory of Medical Genetics, Central South University, Changsha, China; 2Department of Ophthalmology, The Second Xiangya Hospital, Central South University, Changsha, China; 3The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; 4School of Life Science, Central South University, Changsha, China; 5Key Laboratory of Medical Information Research (Central South University), Changsha, Hunan, China

Purpose: Myopia, or near-sightedness, is one of the most common human visual impairments worldwide, and high myopia is one of the leading causes of blindness. In this study, we investigated the mutation spectrum of ZNF644, a causative gene for autosomal dominant high myopia, in a high-myopia cohort from a Chinese population.

Methods: DNA was isolated with the standard proteinase K digestion and phenol-chloroform method from a case cohort of 186 subjects diagnosed with high myopia (spherical refractive error equal or less than −6.00 diopters). Sanger sequencing was performed to find potential mutations in all coding exons, flanking splicing sites, and untranslated regions (UTRs) of ZNF644 (NM_201269). Identified novel variants were further screened in 526 ethnically matched normal controls. Functional prediction and conservation analysis were performed using ANNOVAR.

Results: Five novel variants were identified. Three are missense (c.1201A>G:p.T401A, c.2867C>G:p.T956S, c.3833A>G:p.E1278G), one is synonymous (c.2565A>G:p.T855T), and one (c.-219C>A) is located in the 5′ UTR. Functional prediction indicates that c.3833A>G:p.E1278G was predicted to be damaging by SIFT and Polyphen2. Conservation analysis using PhyloP and GERP++ indicate all of the missense variants are highly conserved. None of these novel mutations was identified in 526 normal controls.

Conclusions: ZNF644 is associated with high myopia in a cohort from a Chinese population. ZNF644 mutations have a minor contribution to the genetic etiology of high myopia.

Myopia, characterized by refraction error, is the most common ocular disorder in the world [1]. The prevalence varies across countries. Multiple studies have reported an approximate prevalence rate of 17% in Australia, 26% in the United States, and 27% in Western Europe [2]. The prevalence in Asian countries, such as China, Singapore, and Japan, is even higher, estimated at about 71% to 96% [3-5]. With high prevalence, myopia causes a serious social burden, and the economic impact is substantial [6,7].

Myopia is usually divided into two groups classified by the degree of refraction error. One is common myopia with low or moderate refractive error, and the other is high myopia [8]. Patients with high myopia have a spherical equivalent refractive error more than or equal to −6.0 diopter sphere (DS) and an axial length longer than or equal to 26.0 mm. High myopia may also present retinal pathological changes and ocular comorbidities, such as macular choroidal degeneration, retinal detachment, premature cataract, and glaucoma; therefore, high myopia is also called pathological or degenerative myopia.

Epidemiology studies have shown that genetic and environmental factors contribute the development of myopia [9]. Twin and family studies have demonstrated that myopia, especially high myopia, has a high heritability [10,11]. A dozen linkage regions and several genome-wide significant associated loci have been identified in families with high myopia and case-control cohorts [12-19]. Familial high myopia is usually inherited as a monogenic disorder, and three inheritances have been found, including autosomal dominant (AD), autosomal recessive (AR), and X-linked inheritance. AD inheritance is the most common. Recently, using whole exome sequencing, Shi et al. identified a causative gene in a Chinese family with AD high myopia, and replicated their results in a sporadic cohort [20]. Subsequently, Tran-Viet et al. performed mutation screening in an American cohort for ZNF644 (gene ID:64146, OMIM number: 614159), and identified a novel missense mutation, which supports that ZNF644 may be a causative gene for high myopia [21]. ZNF644 is a zinc finger protein that functions as a transcriptional factor. In this study, we attempted to replicate the results and enlarge
| ZNF644 exon | Forward | Reverse | Product size (base pair) |
|------------|---------|---------|-------------------------|
| Exon 1     | CATGCCATGTGCTTGGGTCT | AAAATGCGTCTTTTGGATG | 595                     |
| Exon 2     | TGATGGTATCTGGTTGAATGG | TCAACTGGACCAAGTGTGTC | 374                     |
| Exon 3.1   | TGTTGCCTAGCATGAAGAACA | CCATCTCACCACCTCTAC | 850                     |
| Exon 3.2   | TCCCCACCATCCTCCTAT | GGGGTAGAATGATGGCTCTTC | 676                     |
| Exon 3.3   | GTGGATGCCTTCCAACATCT | AATGCAAGTACTCCGTGTGC | 760                     |
| Exon 3.4   | GCCAGTGGATAAAATGCCCTA | CAAGTCTTTCCCCTCAACAG | 832                     |
| Exon 3.5   | AGACCTCTCATAAGCTGACG | TCAACCAACCACCAAGAG | 964                     |
| Exon 4.1   | GGATGATTTGCGGTGATAGG | CTGGGCAGTCTGTTTTGT | 569                     |
| Exon 4.2   | TCCCCAGACCTTGGATGCTC | CCAAGAAAGGACACAGAGA | 600                     |
| Exon 5     | TAGGGAATGAATGCCGACT | ACACCTGGCCAAGCTACTTT | 494                     |
| Exon 6.1   | TGCTCCACCTATACAAAGATT | TGGCTGCTTACATGCTGTC | 683                     |
| Exon 6.2   | AGCCAGTTTGAATGGATGT | TAGCATGGATGCACACACTT | 699                     |
| Exon 6.3   | TGTTCACTCAAATAGGCGAGAG | CATGACCAAGACACCTGCAC | 688                     |
| Exon 6.4   | ACAGGACAGGTTTGCTCTT | TCCAATGAAACACAACTGAAG | 697                     |
the mutation spectrum of ZNF644 in a separate Chinese high myopia cohort.

METHODS

Study subjects: Subjects from Hunan and Henan province with a spherical refractive error of −6.00 diopters (D) or less were collected as high myopia cases. A total of 186 cases (88 males and 98 females, the average age is 38 between 4 and 74) were recruited and accepted clinical examination and blood collection with informed consent. All of the affected cases have a history of myopia onset before 10 years of age. A comprehensive ophthalmic examination was performed, and the refractive error and axial length were measured and recorded. All of the affected individuals have no known ocular disease or insult that could predispose them to myopia, such as retinopathy of prematurity or early-age media opacification, and known genetic diseases associated with myopia, such as Stickler or Marfan syndrome, were excluded. We also collected 526 population-matched subjects with no any ocular malformation and high-myopia family history as a normal control cohort. The study was approved by the Institutional Review Board of the State Key Laboratory of Medical Genetics and adhered to the tenets of the Declaration of Helsinki.

PCR and resequencing: Genomic DNA was extracted from leukocytes from 5 ml of peripheral blood from all individuals with the standard proteinase K digestion and phenol-chloroform method. PCR primer pairs for ZNF644 (NM_201269) spanning all exons, splicing sites, and untranslated gene regions (UTRs) were designed by the online program Primer3. In total, 14 primer pairs were selected to cover all exons, UTRs, and intron-exon boundaries. Primers were provided in Table 1. PCR was performed in a touchdown procedure. The first phase: 95 °C 30 s denaturation, 65 °C 30 s (0.5 °C touchdown every cycle) annealing, 72 °C 30 s extension, for a total of 10 cycles. The second phase: 95 °C 30 s, 60 °C 30 s, 72 °C 30 s, for a total of 22 cycles. A 95 °C 5 min (hotstar) for the first cycle and 72 °C 10 min for the final cycle. Amplified products were separated with polyacrylamide gel electrophoresis (PAGE) and visualized with

| Table 2. Summary of the refractive error and axial length for the 186 patients in this study. |
|---------------------------------------------|
| Category | Age | Refractive Error [DS] | Axial Length [mm] |
|          |     | OD      | OS      | OD      | OS      |
| Min      | 3    | 6.40    | 6.50    | 26.50   | 26.20   |
| Max      | 77   | 30.00   | 30.00   | 44.38   | 35.00   |
| Mid      | 41   | 11.75   | 12.00   | 27.52   | 27.46   |
| Avg      | 39   | 13.64   | 14.31   | 28.07   | 27.99   |

| Table 3. All variations identified in 186 high myopia cases. |
|-------------------------------------------------------------|
| Variants*         | Amino acid change | Exonic function | Number case (n=186) | Number control (n=526) | MAF in 1000 genome project | Snp ID     |
| c.+1250T>A        | NA                | UTR3             | 32                  | NA                   | 0.09645               | rs17131232 |
| c.+1015T>C        | NA                | UTR3             | 13                  | NA                   | 0.02284               | rs76101054 |
| c.+676C>T         | NA                | UTR3             | 85                  | NA                   | 0.1421                | rs1188952  |
| c.3833A>G         | p.E1278G          | Missense         | 1                   | 0                    | 0                     | Novel      |
| c.3266A>G         | p.Y1089C          | Missense         | 1                   | NA                   | 0.01015               | rs193167060|
| c.2867C>G         | p.T956S           | Missense         | 1                   | 0                    | 0                     | Novel      |
| c.2565A>G         | p.T855T           | Synonymous       | 1                   | 0                    | 0                     | Novel      |
| c.1338G>A         | p.R446R           | Synonymous       | 1                   | NA                   | 0.002538              | rs200221992|
| c.1212C>T         | p.T404T           | Synonymous       | 5                   | NA                   | 0.01523               | rs41286763 |
| c.1201A>G         | p.T401A           | Missense         | 1                   | 0                    | 0                     | Novel      |
| c.913G>A          | p.E305K           | Missense         | 4                   | NA                   | 0.01523               | rs149597385|
| c.-219C>A         | NA                | UTR5             | 3                   | 0                    | 0                     | Novel      |

Note: a. nucleotide and amino acid position is according to isoform NM_201269; b. minor allele frequency in Chinese population (CHB and CHS) from 1000 genome project data released in April, 2012.
silver staining. Sequencing was performed on both strands of each amplicon with the ABI PRISM3100 automated DNA sequencer (Life Technologies, Carlsbad, CA). Sequences were analyzed using the Seqman program to detect variants, and compared against the Reference Sequence. All sequences were visualized. A sequence reaction was considered successful if the sequence contained high-quality base calls for at least 90% of the bases. If a sequence failed the quality control, resequencing was performed. Association analysis was performed with the chi-square test or Fisher’s exact test in R. Functional prediction and conservation analysis were performed using ANNOVAR.

RESULTS

All subjects with high myopia are from a Chinese population and received full ophthalmologic examinations before being included. The average refractive error of the 186 patients with high myopia was −13.10 DS for the right eye (OD) and −12.39 DS for the left eye (OS), and ranged from −6.00 DS to −30.00 DS (OD) and −6.25 DS to −30.00 DS (OS). The average axial length was 28.18 mm for the right eye (OD) and 28.16 mm for the left eye (OS), and ranged from 26.17 mm to 44.38 mm (OD) and 26.2 mm to 44 mm (OS). Further detailed clinical information is summarized in Table 2.

Thirteen variants were identified (Table 3). Five are novel variants that are not reported in dbSNP137, 1000 Genomes, and NHLBI ESP6500 exome sequencing data (Table 3, Figure 1). All of these novel variants were also evaluated in 526 population-matched normal controls, and none were identified in the control individuals. Functional prediction using SIFT and Polyphen2 indicated that p.T401A and p.T956S were either tolerant or benign, whereas p.E1278G was predicted to be damaging by SIFT and Polyphen2 (Table 4). Although p.T401A and p.T956S were not predicted to be damaging, conservation analysis using PhyloP and GERP++ indicated that all are highly conserved (Table 4). The missense and synonymous mutations were identified in only one patient; however, the mutation located in the 5′ UTR was identified in three patients. The phenotypes of the cases with the novel variants are serious. All had refractive error more than −10 DS, except one case (M21787) whose refractive errors were −7.5 DS for right eye and −9 DS for left eye. Detailed clinical information for the patients with these novel variants is described in Table 5.

To test whether the identified common SNPs with minor allele frequency (MAF) larger than 1% (rs17131232, rs76101054, rs1188952, rs193167060, rs41286763, rs149597385, Table 3) are associated with high myopia, we performed
| Variants  | AAChange  | ExonicFunc | dbSNP137 | SIFT\(^a\) | PolyPhen\(^b\) | PhyloP\(^c\) | GERP++   | Study\(^d\) |
|----------|-----------|------------|----------|-------------|----------------|-------------|----------|-------------|
| c.:+12C>G | -         | UTR3       | Novel    | NA          | NA             | NA          | NA       | Shi, et al. [20] |
| c.:+592G>A| -         | UTR3       | Novel    | NA          | NA             | NA          | NA       | Shi, et al. [20] |
| c.3833A>G | p.E1278G  | Missense   | Novel    | D           | D              | C           | 4.42     | This study   |
| c.2867C>G | p.T956S   | Missense   | Novel    | T           | B              | C           | 4.7      | This study   |
| c.2565A>G | p.T855T   | Synonymous | Novel    | NA          | NA             | NA          | NA       | This study   |
| c.2096G>A | p.C699Y   | Missense   | Novel    | T           | D              | C           | 4.72     | Shi, et al. [20] |
| c.2038C>G | p.R680G   | Missense   | Novel    | D           | D              | C           | 4.27     | Shi, et al. [20] |
| c.2014A>G | p.S672G   | Missense   | Novel    | D           | P              | N           | 1.31     | Shi, et al. [20] |
| c.1759A>T | p.S87L    | Missense   | Novel    | T           | B              | N           | −8.99    | Shi, et al. [20] |
| c.1201A>G | p.T401A   | Missense   | Novel    | T           | B              | C           | 4.01     | This study   |
| c.821A>T  | p.E274V   | Missense   | Novel    | D           | B              | C           | 5.44     | Tran-Viet, et al. [21] |
| c.-219C>A | -         | UTR5       | Novel    | NA          | NA             | NA          | NA       | This study   |

Notes: a. D represents damaging, T represents tolerant; b. D represents damaging, B represents Benign; c. C represents conservation, N represents non conservation; d. Three studies have been performed to investigate ZNF644 mutations and high myopia including this one. Shi, et al. refer to reference 20 and Tran-Viet, et al. refer to reference 21.
association analysis using 197 Chinese subjects (CHB, CHS) who had no phenotype record from the 1000 Genome project as the controls. Unfortunately, we failed to find an association of these polymorphisms between the patients with high myopia and the controls (rs17131232: p=0.81; rs76101054: p=0.43; rs1188952: p=0.06; rs193167060: p=0.37; rs41286763: p=1.00; rs149597385: p=0.75).

**DISCUSSION**

We performed a mutation screening of ZNF644 in a separate high-myopia cohort from a Chinese population, and identified five novel variants that had not been reported in dbSNP137, 1000 Genomes, and NHLBI ESP exome in seven patients. All of the variants were also absent in 526 population-matched normal controls. These novel variants were all identified in sporadic cases.

Until now, three studies, including this study, have investigated the mutations of ZNF644 in patients with high myopia [20, 21]. A total of 12 novel variants have been identified (Table 5). Three were identified in the 3′ UTR, nine were identified in coding regions (one synonymous and eight missense), and one was identified in the 5′ UTR. Functional prediction for the missense variants demonstrated that p.E1278G, p.R680G, p.E274V, and p.C699Y were predicted to be damaging by either SIFT or PolyPhen2 or both; however, p.T956S, p.I587L, and p.T401A were predicted to be either benign or tolerant. Conservation analysis revealed that p.E1278G, p.T956S, p.R680G, p.E274V, p.C699Y, and p.T401A are conserved, but p.S672G and p.I587L failed to survive the conservation threshold (Table 4). Variants p.I587, p.C699Y, c.+592G>A, and c.-219C>A were recurrently identified in more than one case. All variants were identified in sporadic cases except p.S672G, which was identified and cosegregated with the phenotype in a large family with high myopia [20].

Genetic studies have revealed that high myopia has an extremely high genetic heterogeneity. For example, 19 linkage peaks have been identified up to now, and most cannot be replicated in independent study; a genome-wide association study also revealed dozens of risk variants or susceptible genes [22]. Mutations of genes identified in Mendelian inheritance families and sporadic cases, such as ZNF644, SCO2 (gene ID:9997, OMIM number: 604272), LRPAP1 (gene ID:4043, OMIM number: 104225), and LEPREL1 (gene ID:55214, OMIM number: 610341), explain only a small proportion of the subjects with high myopia [23-25]. Therefore, ZNF644 mutations identified in sporadic patients with high myopia must be evaluated in a larger cohort of patients with well-characterized high myopia and normal controls to determine whether these variants are associated with the clinical outcome or not.

ZNF644 encodes zinc finger transcription factor, which is ubiquitously expressed in several tissues such as the eye, liver, and placenta. The biologic function and the mechanism of this gene in high myopia pathogenesis are still unclear, although this gene was revealed to be associated with high myopia three years ago. Further studies should be conducted to investigate the functional consequence of these mutations, or at least the mutation cosegregating with high myopia in the large family (p.S672G). An animal model study should also be conducted to analyze the phenocopy and molecular mechanism of ZNF644 in the development of myopia.

**ACKNOWLEDGMENTS**

We greatly thank all the patients who participated in this study. This work was supported by National Basic Research Program of China (2012CB517902), National Natural Science Foundation of China (81330027, 81161120544) and Fundamental Research Funds for the Central Universities (2012zzts110). Co-Corresponding authors should be

**Table 5. Refractive error and axial length information for the patients with novel mutations in this study.**

| Individual | Sex | Age (Year) | Onset (Yr) | refractive error | axial length (mm) | Variants |
|------------|-----|------------|------------|------------------|------------------|----------|
|            |     |            |            | OD^a | OS^a | OD | OS |          |         |
| M20366     | F   | 52         | Before 10  | -14.00 | -15.00 | 28 | 28.5 | c.-219C>A |
| M21787     | F   | 28         | 9          | -7.50  | -9.00  | 27 | 28  | c.-219C>A |
| M21792     | F   | 51         | 10         | -10.00 | -10.00 | 27 | 28  | c.-219C>A |
| M16354     | F   | 40         | Before 8   | -15.00 | -15.00 | 28.5 | 29 | c.1201A>G |
| M21315     | F   | 65         | Before 8   | -20.00 | -19.00 | 30 | 30  | c.2565A>G |
| M21325     | F   | 48         | 7          | -20.00 | -18.00 | 29.5 | 29  | c.2867C>G |
| M21320     | M   | 37         | Before 10  | -17.50 | -10.00 | 28.5 | 27  | c.3833A>G |

Note: a. OD represents right eye; b. OS represents left eye.
addressed to Zhengmao Hu (huzhengmao@sklmg.edu.cn) or Kun Xia (xiakun@sklmg.edu.cn). All of the authors declare no conflict of interest.

REFERENCES

1. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. Am J Ophthalmol 1971; 71:42-53. [PMID: 5099937].

2. Sperduto RD, Seigel D, Roberts J, Rowland M. Prevalence of myopia in the United States. Arch Ophthalmol 1983; 101:405-7. [PMID: 6830491].

3. Sawada A, Tomidokoro A, Arai M, Iwase A, Yamamoto T. Tajimi Study G. Refractive errors in an elderly Japanese population: the Tajimi study. Ophthalmology 2008; 115:363-70. [PMID: 18249304].

4. He M, Zheng Y, Xiang F. Prevalence of myopia in urban and rural children in mainland China. Optom Vis Sci 2009; 86:40-4. [PMID: 19104445].

5. Wong TY, Foster PJ, Hee J, Ng TP, Tielsch JM, Chew SJ, Johnson GJ, Seah SK. Prevalence and risk factors for refractive errors in adult Chinese in Singapore. Invest Ophthalmol Vis Sci 2000; 41:2486-94. [PMID: 10937558].

6. Frick KD, Gower EW, Kempen JH, Wolff JL. Economic impact of visual impairment and blindness in the United States. Arch Ophthalmol 2007; 125:544-50. [PMID: 17420375].

7. Rein DB, Zhang P, Wirth KE, Lee PP, Hoerger TJ, McCall N, Klein R, Tielsch JM, Vijan S, Saaddine J. The economic burden of major adult visual disorders in the United States. Arch Ophthalmol 2006; 124:1754-60. [PMID: 17159036].

8. Young TL. Dissecting the genetics of high human myopia: a molecular biologic approach. Trans Am Ophthalmol Soc 2004; 102:423-45. [PMID: 15747770].

9. Dirani M, Shekar SN, Baird PN. The role of educational attainment in refraction: the Genes in Myopia (GEM) twin study. Invest Ophthalmol Vis Sci 2008; 49:534-8. [PMID: 18234996].

10. Lopes MC, Andrew T, Carbonaro F, Spector TD, Hammond CJ. Estimating heritability and shared environmental effects for refractive error in twin and family studies. Invest Ophthalmol Vis Sci 2009; 50:126-31. [PMID: 18757056].

11. Teikari JM, O'Donnell J, Caprio J, Koskenvuo M. Impact of heredity in myopia. Hum Hered 1991; 41:151-6. [PMID: 19374888].

12. Paluru PC, Nallasamy S, Devoto M, Rappaport EF, Young TL. Identification of a novel locus on 2q for autosomal dominant high-grade myopia. Invest Ophthalmol Vis Sci 2005; 46:2300-7. [PMID: 15980214].

13. Klein AP, Duggal P, Lee KE, Klein R, Bailey-Wilson JE, Klein BE. Confirmation of linkage to ocular refraction on chromosome 22q and identification of a novel linkage region on 1q. Arch Ophthalmol 2007; 125:80-5. [PMID: 17208856].

14. Schwartz M, Haim M, Skarsholm D. X-linked myopia: Bornholm eye disease. Linkage to DNA markers on the distal part of Xq. Clin Genet 1990; 38:281-6. [PMID: 1980096].

15. Nakanishi H, Yamada R, Gotoh N, Hayashi H, Yamashiro K, Shimada N, Ohno-Matsui K, Mochizuki M, Saito M, Iida T, Matsuo K, Tajima K, Yoshimura N, Matsuda F. A genomewide association analysis identified a novel susceptible locus for pathological myopia at 11q24.1. PLoS Genet 2009; 5:e1000660-[PMID: 19779542].

16. Lam CY, Tam PO, Fan DS, Fan BJ, Wang DY, Lee CW, Pang CP, Lam DS. A genome-wide scan maps a novel high myopia locus to 5p15. Invest Ophthalmol Vis Sci 2008; 49:3768-78. [PMID: 18421076].

17. Young TL, Metlapally R, Shay AE. Complex trait genetics of refractive error. Arch Ophthalmol 2007; 125:38-48. [PMID: 17210850].

18. Yu ZQ, Li YB, Huang CX, Chu RY, Hu DN, Shen ZH, Huang W. A genome-wide screening for pathological myopia suggests a novel locus on chromosome 15q21-13. Zhonghua Yan Ke Za Zhi 2007; 43:233-8. [PMID: 17605906].

19. Inamori Y, Ota M, Inoko H, Okada E, Nishizaki R, Shiota T, Mok J, Oka A, Ohno S, Mizuki N. The COL1A1 gene and high myopia susceptibility in Japanese. Hum Genet 2007; 12:151-7. [PMID: 17557158].

20. Shi Y, Li Y, Zhang D, Zhang H, Li Y, Lu F, Liu X, He F, Gong B, Cai L, Li R, Liao S, Ma S, Lin H, Cheng J, Zheng H, Shan Y, Chen B, Hu J, Jin X, Zhao P, Chen Y, Zhang Y, Lin Y, Li X, Fan Y, Yang H, Wang J, Yang Z. Exome sequencing identifies ZNF644 mutations in high myopia. PLoS Genet 2011; 7:e1002084-[PMID: 21695231].

21. Tran-Viet KN, St Germain E, Soler V, Powell C, Lim SH, Klemm T, Saw SM, Young TL. Study of a US cohort supports the role of ZNF644 and high-grade myopia susceptibility. Mol Vis 2012; 18:937-44. [PMID: 22539872].

22. Verhoeven VJ, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, Hohn R, MacGregor S, Hewitt AW, Nag A, Cheng CY, Yonova-Doeng E, Zhou X, Ikram MK, Buutinkhij GH, McMahon G, Kemp JP, Pursain BS, Simpson CL, Makela KM, Lehtimaki T, Kahonen M, Paterson AD, Hosseini SM, Wong HS, Xu L, Jonas JB, Parsissin O, Wedenoja J, Yip SP, Ho DW, Pang CP, Chen LJ, Burdon KP, Craig JE, Klein BE, Klein R, Haller T, Metspalu A, Khor CC, Tai ES, Aung T, Vithana E, Tay WT, Barathia VA. Consortium for Refractive E, Myopia, Chen P, Li R, Liao J, Zheng Y, Ong RT, Doring A, Diabetes C, Complications Trial/Epidemiology of Diabetes I, Complications Research G, Evans DM, Timpson NJ, Verkerk AJ, Meitinger T, Raitakari O, Hawthorne F, Spector TD, Karssen LC, Pirastu M, Murgia F, Ang W, Wellcome Trust Case Control C, Mishra A, Montgomery GW, Pennell CE, Cumberland PM, Cotlarciuc I, Mitchell P, Wang JJ, Schache M, Janmahasatian S, Igo RP, Jr, Lass JH, Chew E, Iyengar SK, Fuchs’ Genetics Multi-Center Study G, Gorgels TG, Rudan I, Hayward C, Wright AF, Polasek O, Vatavuk Z, Wilson JF, Fleck B, Zeller T, Mirshahi A, Muller C, Uitterlinden AG, Rivadeneira F, Vingerling JR, Hofman A, Oostra BA, Amin N, Bergen AA, Teo YY, Rahi
JS, Vitart V, Williams C, Baird PN, Wong TY, Oexle K, Pfeiffer N, Mackey DA, Young TL, van Duijn CM, Saw SM, Bailey-Wilson JE, Stambolian D, Klaver CC, Hammond CJ. Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. Nat Genet 2013; 45:314-8. [PMID: 23396134].

23. Aldahmesh MA, Khan AO, Alkuraya H, Adly N, Anazi S, Al-Saleh AA, Mohamed JY, Hijazi H, Prabakaran S, Tacke M, Al-Khrashi A, Hashem M, Reinheckel T, Assiri A, Alkuraya FS. Mutations in LRPAP1 Are Associated with Severe Myopia in Humans. Am J Hum Genet 2013; 93:313-20. [PMID: 23830514].

24. Mordechai S, Gradstein L, Pasanen A, Ofir R, El Amour K, Levy J, Belfair N, Lifshitz T, Joshua S, Narkis G, Elbedour K, Myllyharju J, Birk OS. High myopia caused by a mutation in LEPREL1, encoding prolyl 3-hydroxylase 2. Am J Hum Genet 2011; 89:438-45. [PMID: 21885030].

25. Tran-Viet KN, Powell C, Barathi VA, Klemm T, Maurer-Stroh S, Limviphuvadh V, Soler V, Ho C, Yanovitch T, Schneider G, Li YJ, Nading E, Metlapally R, Saw SM, Goh L, Rozen S, Young TL. Mutations in SCO2 are associated with autosomal-dominant high-grade myopia. Am J Hum Genet 2013; 92:820-6. [PMID: 23643385].

Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 30 June 2014. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.