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New *ZNF644* mutations identified in patients with high myopia

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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

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Table 1. Primers for PCR and sequencing of ZNF644.

ZN644 exon	Forward	Reverse	Product size (base pair)
Exon 1	CATGCCTAGTGCTTGGGTCT	AAAATGCGTCCTTTTGGATG	595
Exon 2	TGATGGTATTCTGGTTGAATGG	TCAACTGGACCAAGTGTGTCA	374
Exon 3.1	TGTTGCCTAGCATGAAGAACA	CCATCCTCACCCACCTCTAC	850
Exon 3.2	TCCCACCCATTCCAATAAAA	GGGGTAGAATGATGGCTCTTC	676
Exon 3.3	GTGGATGCCTTCCAACATCT	AATGCAAGTACTCCGTGTGC	760
Exon 3.4	GGCAGTGGTAAAATGCCCTA	CAAGTCTTCCCCTCCAACAG	832
Exon 3.5	AGACCCTCATAAGCCTGACG	TCAAACCAACCACCACAGAG	964
Exon 4.1	GGATGATTTGGGCTGATAGG	CTGGGCAGTTCTGGTTTTGT	569
Exon 4.2	TTCCCAGACCATTTGTAGCTC	CCAAGAAAAGAGGCACAGAGA	600
Exon 5	TAGGGAAATGAATGCGGACT	ACACCTGGCCAAGCTACTTT	494
Exon 6.1	TGCTCCCACCTATACAAAGATT	TGGCTGCTTACATGTACTGCTC	683
Exon 6.2	AGCCAGTTTGAATTGGATGT	TAGCATGGATGCACCACTTT	699
Exon 6.3	TGTTCACTCAAATAGGGCAGAG	CATGACCAAGACACCTGCAC	688
Exon 6.4	ACAGGACAGGTTTGCCTCTT	TCCAATGAAACACAACCTGAAG	697

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

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 3. All variations identified in 186 high myopia cases.

Variants[a]	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.

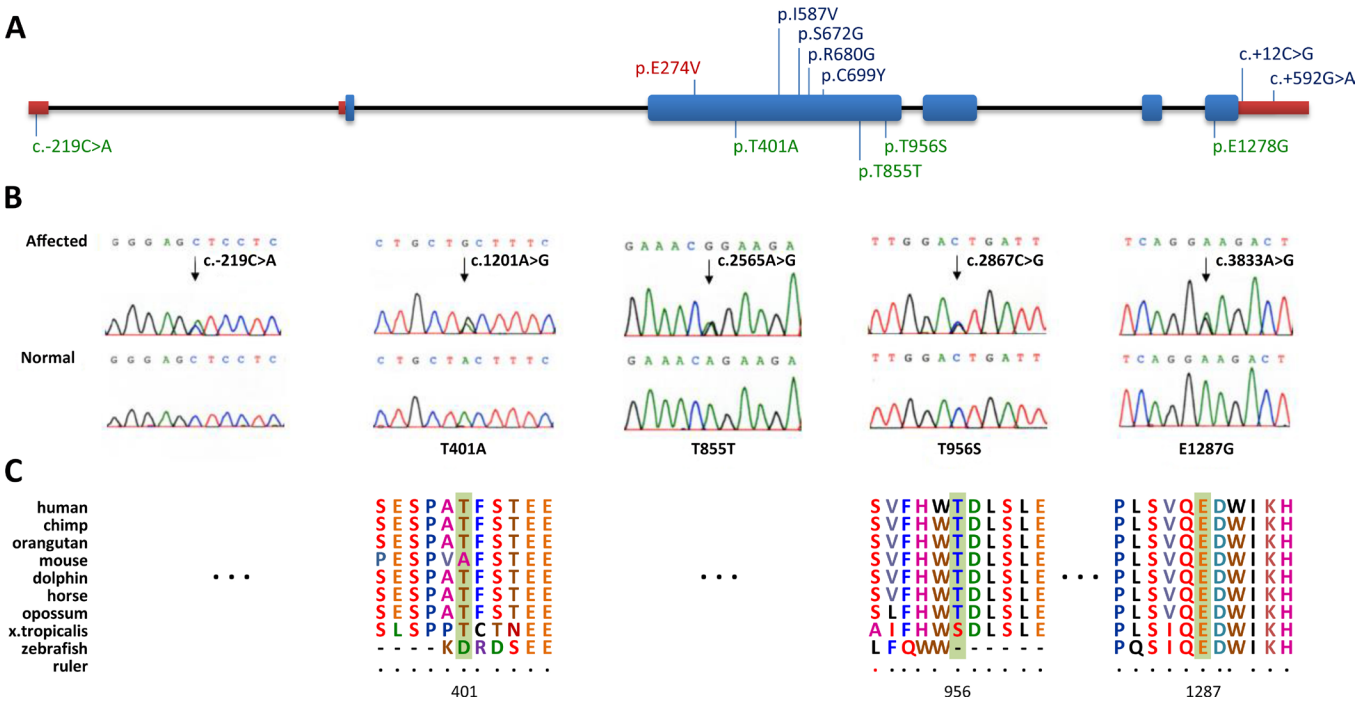

Figure 1. Mutation spectrum of *ZNF644* in patients with high myopia up to now. **A**: Mutation locations in the *ZNF644* DNA sequence. The mutations colored blue were found by Shi et al., the mutation colored red was identified by Tran-Viet et al., and the mutations colored green were identified in this study. **B**: Sequence chromatogram of the novel variants identified in this study compared with the normal controls. **C**: FASTA alignment analysis for the missense mutations identified in this study.

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 −12.39DS 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

Table 4. Mutations of *ZNF644* identified in high myopia patients up to now and the functional and conservation prediction for these mutations.

Variants	AAChange	ExonicFunc	dbSNP137	SIFT[a]	PolyPhen2[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.I587L	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.S672G, 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.

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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[b]	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.

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