MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2023; 29: e937702
DOI: 10.12659/MSM.937702

Received: 2022.07.04
Accepted: 2022.12.12
Available online: 2023.01.03
Published: 2023.01.30

Polymorphisms in *TRIB2* and *CAPRIN2* Genes Contribute to the Susceptibility to High Myopia-Induced Cataract in Han Chinese Population

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Financial support: None declared
Conflict of interest: None declared

Background: Myopia has been shown to be associated with many pathological complications including cataracts, and previous evidence supported that high myopia facilitates the formation of cataracts. However, no studies have identified a link between the genetic susceptibility of high myopia-induced cataracts (HMC) and the underlying genetic mechanisms. Our study aimed to determine how the *TRIB2* and *CAPRIN2* genes correlate to the risk of HMC.

Material/Methods: In total, we successfully recruited 3162 participants, including 1026 participants with high myopia and cataracts and 2136 controls with high myopia only. For genotyping, 22 tag single nucleotide polymorphisms (SNPs) in *TRIB2* and *CAPRIN2* genes were chosen. Single marker association analysis and functional effects of significant SNPs were carried out.

Results: Strong correlation signals were captured for SNP rs890069 (χ^2=22.13, P=2.55×10^{-6}) in *TRIB2* and SNP rs17739338 (χ^2=16.07, P=6.10×10^{-5}) in *CAPRIN2*. In patients with high myopia, the C allele at SNP rs890069 was strongly linked to cataract risk (OR [95% CI]=1.36 [1.20-1.55]). In patients with high myopia, the T allele at SNP rs17739338 was significantly related to a lower risk of cataract (OR [95% CI]=0.54 [0.40-0.74]). In different types of human tissues, SNPs rs890069 and rs17739338 were found to be significantly correlated to the levels of *TRIB2* and *CAPRIN2* gene expression.

Conclusions: Our study indicated that both *TRIB2* and *CAPRIN2* genes conferred the susceptibility to cataract in patients with high myopia and Chinese Han ancestry. Future research remains necessary for fully understanding the pathogenic mechanisms and genetic characteristics of cataract.

Keywords: Case-Control Studies • Disease Susceptibility • Polymorphism, Single Nucleotide

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Background

Cataracts leads to great harm of vision and disability in patients, accounting for more than 33.3% of blindness worldwide [1-3]. Other than being affected by risk factors such as age-related degenerative changes in the crystalline lens [4-6], the development of cataracts is strongly influenced by hereditary factors, as shown by twin and genealogy research [7,8]. The heritability of cataracts is approximately 35% to 58% [9]. Although previous studies have uncovered many risk gene variants for cataracts [10], the genetic underpinnings of the pathogenesis of cataracts remain confusing. Myopia affects hundreds of millions of people worldwide, and it has become more commonplace in recent years. According to a recent study, myopia prevalence would increase to 49.8% and high myopia prevalence to 9.8% by 2050 [10]. Myopia has been shown to be associated with many pathological complications, including cataracts [11]. Previous evidence supported that high myopia facilitates the formation of cataracts [12]. Myopia is also coregulated by genetic and environmental factors [13]. Thus, genetic factors are indicated to contribute to the pathogenesis of high myopia-induced cataracts (HMC). However, to date, few studies have revealed the association between the genetic susceptibility of HMC and the underlying genetic mechanisms.

Caprin Family Member 2 (CAPRIN2) is a type of RNA binding protein. CAPRIN2 is implicated in RNA transportation and cell differentiation and was shown to activate the Wnt pathway, suggesting that it is involved in the development of hepatoblastoma [14]. In addition, CAPRIN2 was found to be located at the rim of the lens vesicles and to be implicated in eye development and disease. In animal models, Caprin2 has been shown to be a component of RNA granules of the lens and contributes to the posttranscriptional regulation of gene expression in eye morphogenesis. Mice with *Caprin2* gene knockout showed abnormal compact lens nuclei and developmental defectsin the lens [15]. In flies, the Drosophila ortholog of Caprin2 was associated with RNA granules and eye sizes [16,17]. Thus, the *CAPRIN2* gene may constitute a liability in the development of cataracts. Single nucleotide polymorphism (SNP) rs17739338 in the *CAPRIN2* gene was recently reported to be significantly correlated with susceptibility to cataracts in Europeans [9].

Tribbles pseudokinase 2 (TRIB2) is one of the pseudokinase proteins in the serine/threonine kinase superfamily. TRIB2 is involved in the processes of cell growth, proliferation, and differentiation in the contexts of normal development and in stressful stimuli [18]. TRIB2 is an upstream molecule of PI3K/AKT/MAPK signaling, and dysfunction of TRIB2 has been shown to be related to many tumors [19,20]. In addition, with a potential role in cell development in the ocular region, the *TRIB2* gene may also be associated with ophthalmic diseases such as cataracts. A current meta-analysis of genome-wide association studies in cataracts found for the first time that SNP rs890069 near the *TRIB2* gene was positively related to the risk of cataracts in Europeans.

Together, the *CAPRIN2* and *TRIB2* genes were reported to be positively related to HMC in Europeans, but those positive signals lack precise biological interpretation, leaving the genetic basis of the HMC unexplained and urgently in need of clarification. The *CAPRIN2* and *TRIB2* genes are 2 significant options for identifying the risk genetic variations in HMC, given the effects of genetic and environmental factors on the pathogenesis of HMC. Therefore, the purpose of our study was to assess the association between both genes and HMC susceptibility in the Chinese Han population.

Material and Methods

Study Participants

We enrolled 1026 high myopia patients with cataracts and 2136 controls (age-matched) with only high myopia from Xi'an Fourth Hospital (**Figure 1**). All participants were high myopia patients and unrelated Han Chinese individuals (at least all 3 generations were of Han descent and had no history of migration). All participants were examined by detailed ophthalmic assessments. According to the spherical equivalent (SE) of both eyes, high myopia was defined by SE ≤-6.0 dioptres (D). Those having both eyes meeting the criteria were included. Those with prior ocular surgery, ocular trauma, strabismus, corneal or ocular surface diseases, corneal scar, uveitis, glaucoma, or other major eye diseases affecting the accuracy of refraction were excluded from the study. Ocular lens opacification and best-corrected visual acuity less than 20/40 were used to diagnose cataracts. According to the lens opacity area of the enrolled patients, cataracts were divided into 4 types: cortical cataracts, nuclear cataracts, posterior subcapsular cataracts, and mixed cataracts. If the enrolled patient had at least 1 eye with more than 1 type of cataract or 2 eyes with different types, he or she was defined as the mixed type. Patients meeting the following criteria were included in the case group: (1) lens opacity; (2) under 50 years old (excluding age-related cataracts); (3) best-corrected visual acuity below 20/40; and (4) no other clear causes of cataracts. Patients with complicated cataracts caused by diabetes or other known causes, as well as with pseudophakia or aphakia in either eye, were also excluded from the study.

The study participants' peripheral blood samples were drawn, conserved, and used in subsequent genotyping. **Table 1** displays the clinical features and demographic data of the study participants that were gathered through questionnaires and medical records. Each participant provided their written informed consent. The Medical Ethics Committee of Xi'an Fourth Hospital approved the study.

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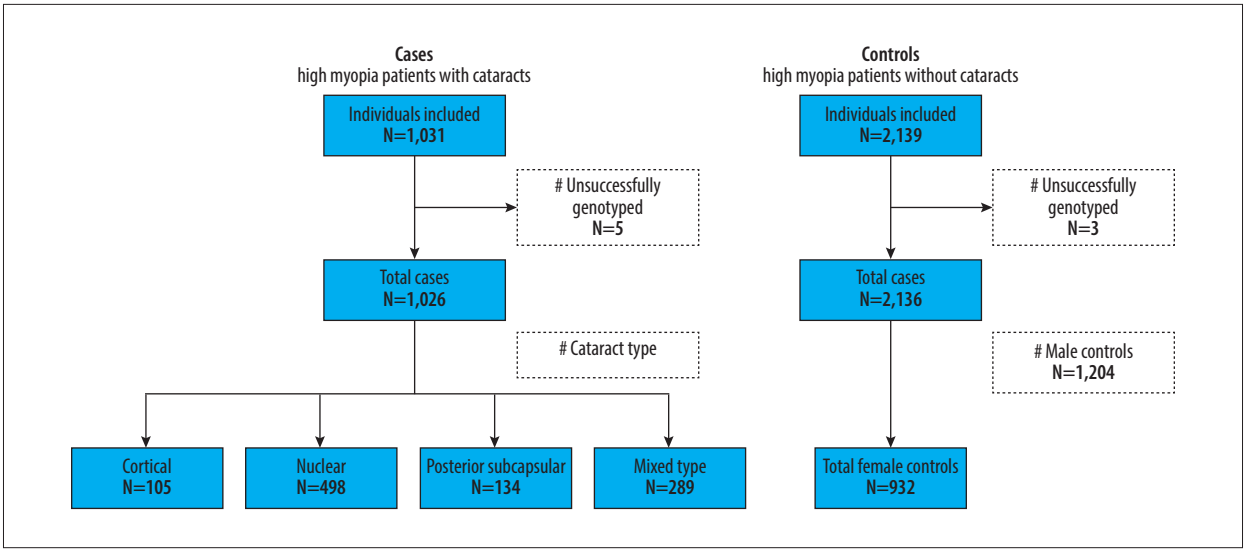

Figure 1. Flow chart of enrolled participants. The figure was made by PowerPoint, Microsoft Office v2017.

Table 1. Clinical and demographic information of the participants.

Variables	Patients with high myopia and cataract (N=1,026)	Patients with high myopia only (N=2,136)	Statistics	*P*-value
Gender (%)				
Male	578 (56)	1204 (56)		
Female	448 (44)	932 (44)	χ^2=0	1.00
Age, years	40.3±6.5	40.4±8.3	*t*=-0.34	0.73
Axial length, mm	26.9±1.1	26.9±1.1	*t*=-0.72	0.47
Cataract type (%)				
Cortical	105 (10)	–	–	–
Nuclear	498 (49)	–	–	–
Posterior subcapsular	134 (13)	–	–	–
Mixed Type	289 (28)	–	–	–

SNP Selection and Genotyping

SNPs in *TRIB2* and *CAPRIN2* genomic regions were extracted for genotyping experiments. For the *TRIB2* gene region, 43 SNPs with minor allele frequency ≥0.02 were screened from 1000 Genomes data. Among these SNPs, 9 tag SNPs were selected using r^2=0.5 as criteria. A similar SNP selection strategy was applied to the *CAPRIN2* gene region. A total of 101 SNPs with minor allele frequency ≥0.02 were extracted, and 13 tag SNPs were selected. Finally, 22 tagging SNPs were chosen in total to be genotyped (**Table 2**).

DNA extractions were carried out from the collected peripheral blood by genomic DNA kits (Axygen Scientific Inc, USA). All screened tag SNPs were detected by the Sequenom MassARRAY platform. Further data processing was conducted using a Typer Analyzer. Technicians were blinded to the sample labels throughout the experiments.

Statistical Analysis

Demographic and clinical information were compared between the case and control groups. The Hardy-Weinberg equilibrium test was carried out in the controls. Haploview was used to display the genotyped SNPs' linkage disequilibrium pattern [21].

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Table 2. The genetic information of the 22 genotyped SNPs.

CHR	POS	SNP	A1	A2	FUNC	Loci	MAF	HWE
2	12723644	rs2278117	G	A	Intron	*TRIB2*	0.19	0.57
2	12724402	rs142350606	G	A	Intron	*TRIB2*	0.07	0.31
2	12727378	rs890069	A	G	Intron	*TRIB2*	0.20	0.88
2	12729487	rs16859293	C	T	Intron	*TRIB2*	0.03	0.68
2	12729652	rs79110076	G	A	Intron	*TRIB2*	0.03	0.72
2	12737341	rs75978038	T	G	Intron	*TRIB2*	0.03	0.68
2	12737483	rs7604252	T	C	Intron	*TRIB2*	0.11	1.00
2	12739026	rs66540381	A	C	Intron	*TRIB2*	0.37	0.96
2	12739432	rs117718684	A	G	Intron	*TRIB2*	0.06	0.47
12	30712277	rs117880663	C	A	Intron	*CAPRIN2*	0.03	0.67
12	30720115	rs12370429	A	G	Intron	*CAPRIN2*	0.35	0.34
12	30723631	rs11051044	A	G	Intron	*CAPRIN2*	0.07	0.37
12	30727816	rs74450722	T	C	Intron	*CAPRIN2*	0.04	0.79
12	30728362	rs6487934	T	C	Intron	*CAPRIN2*	0.28	0.48
12	30731158	rs17739338	A	T	Intron	*CAPRIN2*	0.04	0.34
12	30734886	rs7134998	T	A	Intron	*CAPRIN2*	0.13	0.30
12	30734888	rs201229668	C	T	Intron	*CAPRIN2*	0.04	0.53
12	30737243	rs117381590	T	C	Intron	*CAPRIN2*	0.12	0.84
12	30741023	rs146271709	T	C	Coding-synon	*CAPRIN2*	0.03	0.39
12	30742158	rs148120853	T	A	Intron	*CAPRIN2*	0.03	0.70
12	30747997	rs184106436	G	A	Intron	*CAPRIN2*	0.03	1.00
12	30748333	rs11051056	G	A	Intron	*CAPRIN2*	0.05	0.66

CHR – chromosome; POS – position; A1 – minor allele; A2 – major allele; FUNC – function; MAF – minor allele frequency; HWE – *P*-value for Hardy-Weinberg equilibrium tests conducted in patients with high myopia only.

Single marker association analysis was carried out at the allelic and genotypic levels to assess the genetic relationship between 22 tag SNPs and HMC risk. The statistical significance was examined by χ^2 and Fisher's exact tests. Plink was used for genetic association analysis [22]. To adjust for multiple comparisons, Bonferroni correction was applied. To investigate the potential effects of population stratifications, a Q-Q plot was created. The *P* value cutoff was set at 0.05/22≈0.002 for single marker association analysis. Additionally, we performed an analysis to investigate the correlation of the clinical type of cataract with targeted SNPs.

Several bioinformatics tools were used to further examine the functional effects of the significant SNPs found in association analysis. In the Genotype-Tissue Expression database, the relationship between SNP genotypes and the levels of *TRIB2* and *CAPRIN2* gene expression in different human tissues was investigated [23]. The gene expression of *CAPRIN2* and *TRIB2* in mouse eyes was investigated using the iSyTE database (https://research.bioinformatics.udel.edu/iSyTE/). RegulomeDB was utilized for annotating the significant SNPs for their potential functional significance [24]. In addition, previous associations between the significant SNPs and other complex human traits were explored using the genome-wide association study catalog database [25].

Results

A total of 3162 patients with high myopia, including 1026 patients with both high myopia and cataracts (cases) and 2136 patients with high myopia only (controls), were recruited (**Table 1**). Comparisons between the case and control groups showed no differences in sex (*P*=1.00), age (*P*=0.73), or axial length

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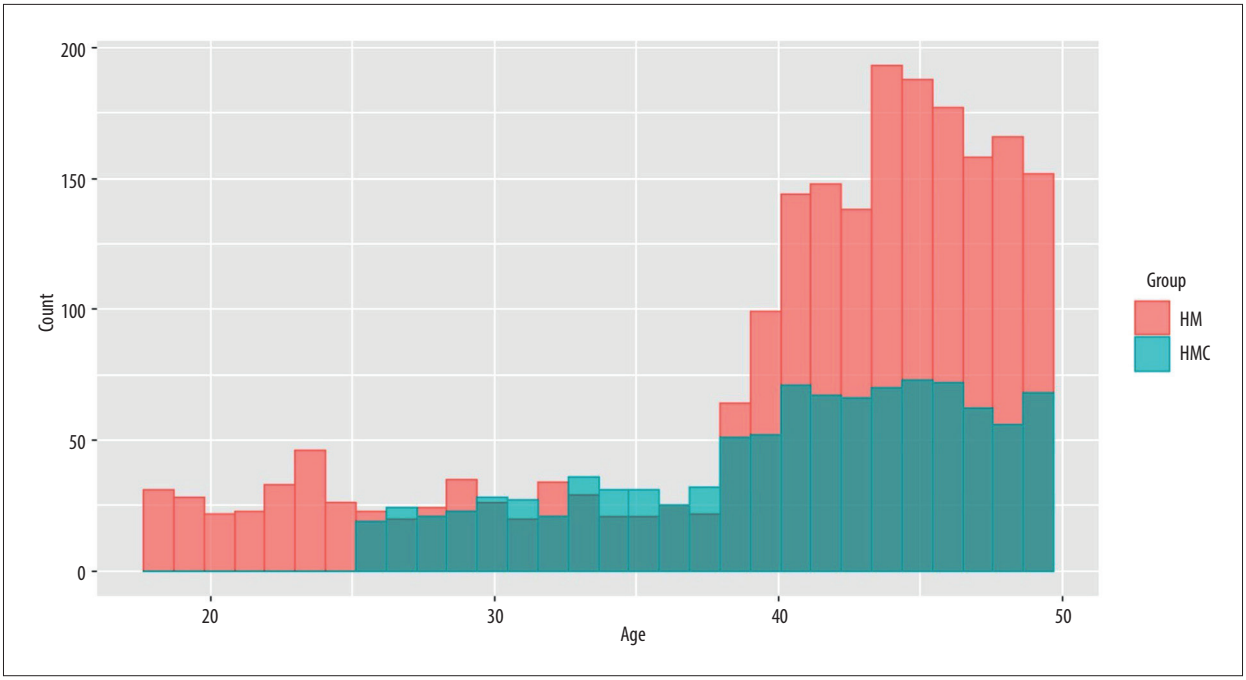

Figure 2. Histogram of age in the HMC and HM groups.

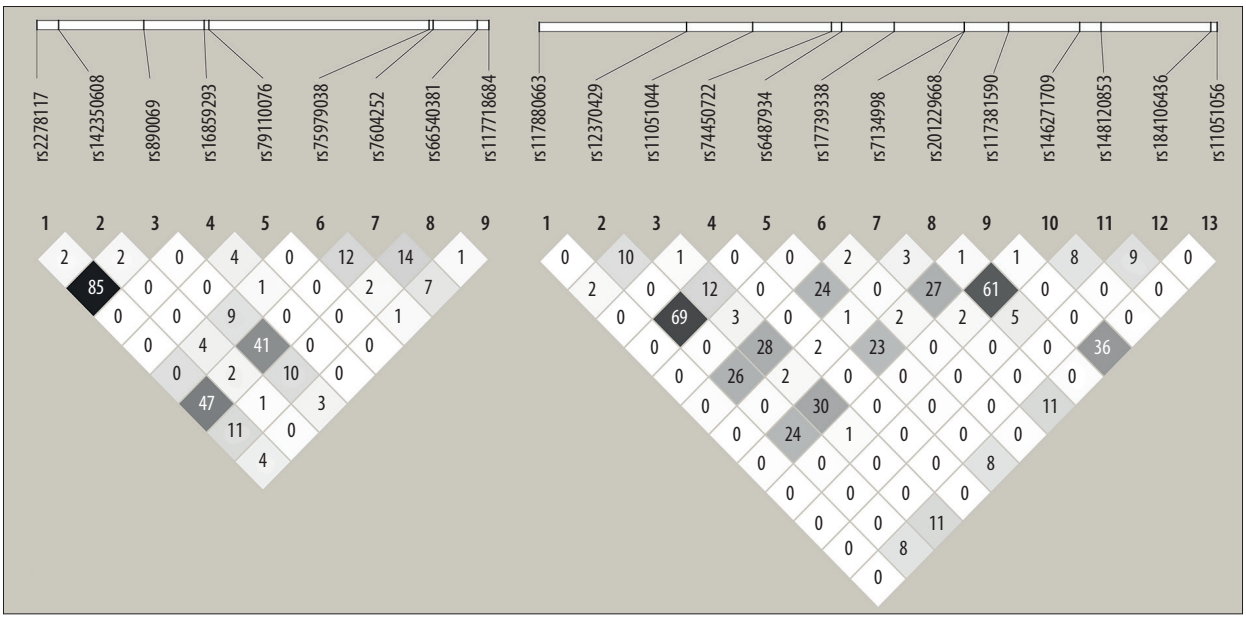

Figure 3. Linkage disequilibrium plot for SNPs genotyped in (**A**) *TRIB2* and (**B**) *CAPRIN2*. The values of r^2 are presented in each cell. The figure was made by Haploview v4.2, manufactured by the Broad Institute.

(*P*=0.47). Among patients with HMC, 105 patients had cortical cataracts (10%), 498 patients had nuclear cataracts (49%), 134 patients had posterior subcapsular cataracts (13%), and 289 patients had mixed-type cataracts (28%). Distributions of age between the 2 groups are shown in **Figure 2**.

All SNPs were in accordance with the Hardy-Weinberg equilibrium in controls (**Table 2**). The LD plot constructed from the genotype data indicated no significant correlations (**Figure 3**). A positive association was identified for SNP rs890069 in *TRIB2* at both genotypic (**Table 3**, χ^2=22.97, P=1.03×10^{-5}) and allelic levels (χ^2=22.13, P=2.55×10^{-6}). The C allele at SNP rs890069 was strongly linked with the risk of cataracts in patients with high myopia (odds ratio [OR] [95% CI]=1.36 [1.20-1.55]). In addition, a dosage-dependent pattern could be observed from the ORs of different genotypes. The OR values increased with

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Table 3. Significant association signals identified from single marker based analyses.

CHR	SNP	POS	Loci	Test	Groups	Patients with high myopia (N=3,162)		OR [95% CI]	*χ^2	*P*-value
						Cataract+ (N=1,026)	Cataract- (N=2,136)			
2	rs890069	12727378	*TRIB2*	GENO	CC	63 (6)	71 (3)	2.07 [1.46-2.95]		
					CT	349 (34)	632 (30)	1.29 [1.10-1.51]		
					TT	614 (60)	1,433 (67)	Ref	22.97	1.03×10^{-5}
				ALLELIC	C	475 (23)	774 (18)	1.36 [1.20-1.55]		
					T	1,577 (77)	3,498 (82)	Ref	22.13	2.55×10^{-6}
12	rs17739338	30731158	*CAPRIN2*	GENO	TT	2 (0.2)	7 (0.3)	0.57 [0.12-2.74]		
					CT	51 (5)	192 (9)	0.53 [0.38-0.73]		
					CC	973 (94.8)	1,937 (90.7)	Ref	–	0.0001
				ALLELIC	T	55 (3)	206 (5)	0.54 [0.40-0.74]		
					C	1,997 (97)	4,066 (95)	Ref	16.07	6.10×10^{-5}

CHR – chromosome; POS – position; GENO – genotypic analysis; ALLELIC – allelic analysis; OR – odds ratio; CI – confidence interval. The values in brackets are percentages. * Fisher exact test was applied when necessary.

increasing copies of the C allele. A strong association was found for SNP rs17739338 in *CAPRIN2* at both genotypic (**Table 3**, $P=1.03\times10^{-5}$) and allelic levels ($\chi^2=16.07$, $P=6.10\times10^{-5}$). The T allele at SNP rs17739338 was significantly related to a lower risk of cataract in patients with high myopia (OR [95% CI]=0.54 [0.40-0.74]). In **Table 4**, the complete outcomes of the single marker association analysis are presented. The locations of both significant SNPs and the gene structures for *CAPRIN2* and *TRIB2* are shown in **Figure 4**.

The Q-Q plot showed that no significant inflations could be identified from the results of the association analysis (**Figure 5**). This indicated that the confounding effects of population stratifications were limited. The significant SNP genotypes and the different clinical types of cataracts did not significantly differ from one another (**Table 5**). Some positive expression quantitative trait loci (eQTL) associations for rs890069 in the *TRIB2* gene were found in 22 out of 47 types of human tissues (**Table 6, Figure 6A**). The most significant signal was obtained from cultured fibroblast cells (NES=-0.11, *T* statistic=-6.30, $P=8\times10^{-10}$). In 34 of the 47 different types of human tissues, there were significant eQTL associations for the rs17739338 in *CAPRIN2* gene (**Table 7, Figure 6B**). Thyroid tissue had the strongest association signal (NES=-0.49, *T* statistic=-13.0, $P=2.10\times10^{-32}$). The expression patterns of Caprin2 (upregulated) and Trib2 (downregulated) are significantly enriched in the lens during the eye development process of mice. It indicates that both genes might play important roles for pathogenesis of eye-related diseases (**Table 8**).

Discussion

We found 2 significant SNPs in the present study, rs890069 in *TRIB2* and rs17739338 in *CAPRIN2*, which are linked to the incidence of cataracts in patients with high myopia in the Chinese Han population. In a recent multi-ethics meta-analysis, both SNPs were identified to be significantly linked to cataract risk [9]. Although the effect size was smaller in the present study than it was in the prior publication, the effect directions of both SNPs were the same. Our findings can be considered as a successful confirmation of these earlier findings in the Chinese Han population.

Since both SNPs were in intronic regions, they could not change the amino acid sequence of the encoded protein to alter its

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Table 4. Full results for single marker based association analyses.

CHR	SNP	A1	A2	Test	Cataract+	Cataract-	χ^2	DF	*P*-value
2	rs2278117	A	G	GENO	37/322/667	71/662/1403	0.24	2	0.89
2	rs2278117	A	G	ALLELIC	396/1656	804/3468	0.21	1	0.65
2	rs142350606	G	A	GENO	7/123/896	13/269/1854	0.29	2	0.87
2	rs142350606	G	A	ALLELIC	137/1915	295/3977	0.11	1	0.74
2	rs890069	C	T	GENO	63/349/614	71/632/1433	22.97	2	1.03×10^{-5}
2	rs890069	C	T	ALLELIC	475/1577	774/3498	22.13	1	2.55×10^{-6}
2	rs16859293	G	A	GENO	2/64/960	2/115/2019	–	–	–
2	rs16859293	G	A	ALLELIC	68/1984	119/4153	1.35	1	0.25
2	rs79110076	A	C	GENO	2/68/956	2/124/2010	–	–	–
2	rs79110076	A	C	ALLELIC	72/1980	128/4144	1.19	1	0.28
2	rs75978038	T	G	GENO	2/49/975	2/115/2019	–	–	–
2	rs75978038	T	G	ALLELIC	53/1999	119/4153	0.22	1	0.64
2	rs7604252	T	C	GENO	16/191/819	23/402/1711	1.33	2	0.51
2	rs7604252	T	C	ALLELIC	223/1829	448/3824	0.21	1	0.65
2	rs66540381	G	A	GENO	134/474/418	287/995/854	0.19	2	0.91
2	rs66540381	G	A	ALLELIC	742/1310	1569/2703	0.19	1	0.66
2	rs117718684	A	G	GENO	2/121/903	6/261/1869	–	–	–
2	rs117718684	A	G	ALLELIC	125/1927	273/3999	0.21	1	0.65
12	rs117880663	A	G	GENO	2/62/962	2/111/2023	–	–	–
12	rs117880663	A	G	ALLELIC	66/1986	115/4157	1.37	1	0.24
12	rs12370429	G	A	GENO	130/462/434	263/944/929	0.41	2	0.82
12	rs12370429	G	A	ALLELIC	722/1330	1470/2802	0.37	1	0.54
12	rs11051044	T	C	GENO	5/131/890	6/265/1865	0.95	2	0.62
12	rs11051044	T	C	ALLELIC	141/1911	277/3995	0.34	1	0.56
12	rs74450722	C	A	GENO	3/86/937	4/171/1961	–	–	–
12	rs74450722	C	A	ALLELIC	92/1960	179/4093	0.29	1	0.59
12	rs6487934	A	G	GENO	77/402/547	173/846/1117	0.48	2	0.79
12	rs6487934	A	G	ALLELIC	556/1496	1192/3080	0.45	1	0.50
12	rs17739338	T	C	GENO	2/51/973	7/192/1937	–	–	–
12	rs17739338	T	C	ALLELIC	55/1997	206/4066	16.07	1	6.10×10^{-5}
12	rs7134998	T	A	GENO	24/232/770	43/478/1615	0.39	2	0.82
12	rs7134998	T	A	ALLELIC	280/1772	564/3708	0.24	1	0.63
12	rs201229668	A	T	GENO	2/64/960	4/150/1982	–	–	–
12	rs201229668	A	T	ALLELIC	68/1984	158/4114	0.60	1	0.44
12	rs117381590	G	A	GENO	12/222/792	32/470/1634	0.62	2	0.73

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Table 4 continued. Full results for single marker based association analyses.

CHR	SNP	A1	A2	Test	Cataract+	Cataract-	χ^2	DF	*P*-value
12	rs117381590	G	A	ALLELIC	246/1806	534/3738	0.34	1	0.56
12	rs146271709	C	T	GENO	2/60/964	2/103/2031	–	–	–
12	rs146271709	C	T	ALLELIC	64/1988	107/4165	1.99	1	0.16
12	rs148120853	T	C	GENO	2/68/956	2/120/2014	–	–	–
12	rs148120853	T	C	ALLELIC	72/1980	124/4148	1.70	1	0.19
12	rs184106436	T	A	GENO	2/53/971	2/128/2006	–	–	–
12	rs184106436	T	A	ALLELIC	57/1995	132/4140	0.47	1	0.50
12	rs11051056	T	C	GENO	3/115/908	4/214/1918	–	–	–
12	rs11051056	T	C	ALLELIC	121/1931	222/4050	1.32	1	0.25

CHR – chromosome; A1 – minor allele; A2 – major allele; DF – degree of freedom; GENO – genotypic analysis; ALLELIC – allelic analysis.

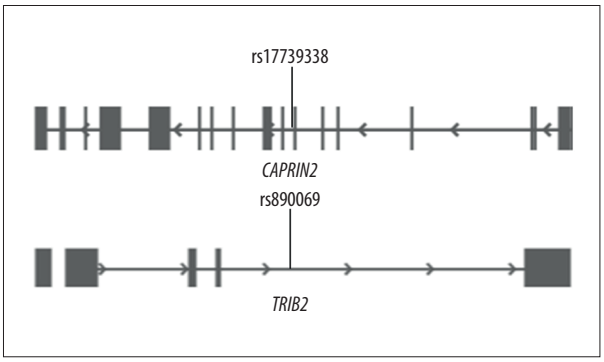

Figure 4. Gene structures of CAPRIN2 and TRIB2 and the locations of SNP rs17739338 and rs890069.

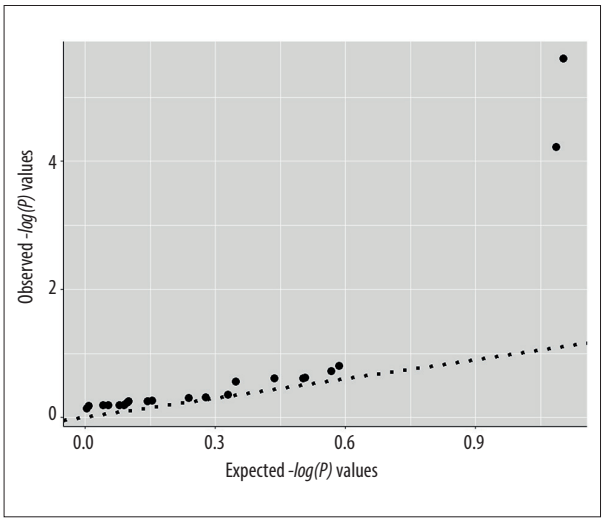

Figure 5. A Q-Q plot for the results of allelic analysis.

molecular structure. Nevertheless, bioinformatics analysis using data from publicly available databases has shown that both SNPs are significantly associated with their mapped genes. Both SNPs showed widespread eQTL signals across many human tissue types. This result suggested that both SNPs may affect gene expression and therefore have functional effects. The Genotype-Tissue Expression database does not include any information on the targeted tissues of cataracts; thus, we need to be wary of these bioinformatics findings.

Table 5. Association between genotypes of targeted SNPs and clinical type of cataract.

Cataract type	Genotypes of rs890069			χ^2	*P*-value	Genotypes of rs17739338			*χ^2	*P*-value
	CC	CT	TT			TT	CT	CC		
Cortical	5	30	70			0	1	104		
Nuclear	30	175	293			1	30	467		
Posterior subcapsular	7	48	79			0	10	124		
Mixed type	21	96	172	3.32	0.77	1	10	278	–	0.09

* Fisher exact test was applied when necessary.

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Table 6. eQTL signals between SNP rs890069 and TRIB2 in multiple types of human tissues.

Gene	Variant ID	SNP	*P*-value	NES	T-statistic	Tissue
TRIB2	chr2_12727378_C_T_b38	rs890069	1.90E-07	-0.16	-5.30	Adipose – Subcutaneous
TRIB2	chr2_12727378_C_T_b38	rs890069	2.20E-07	-0.19	-5.30	Adipose – Visceral (Omentum)
TRIB2	chr2_12727378_C_T_b38	rs890069	6.70E-05	-0.23	-4.10	Adrenal Gland
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0003	-0.16	-3.70	Artery – Aorta
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0780	-0.13	-1.80	Artery – Coronary
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0022	-0.09	-3.10	Artery – Tibial
TRIB2	chr2_12727378_C_T_b38	rs890069	0.3100	-0.08	-1.00	Brain – Amygdala
TRIB2	chr2_12727378_C_T_b38	rs890069	0.5600	0.04	0.59	Brain – Anterior cingulate cortex (BA24)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0030	-0.14	-3.00	Brain – Caudate (basal ganglia)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.4500	0.04	0.76	Brain – Cerebellar Hemisphere
TRIB2	chr2_12727378_C_T_b38	rs890069	0.9900	3.90E-04	0.01	Brain – Cerebellum
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0014	-0.14	-3.20	Brain – Cortex
TRIB2	chr2_12727378_C_T_b38	rs890069	0.3000	-0.06	-1.00	Brain – Frontal Cortex (BA9)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0590	-0.08	-1.90	Brain – Hippocampus
TRIB2	chr2_12727378_C_T_b38	rs890069	0.4800	0.05	0.71	Brain – Hypothalamus
TRIB2	chr2_12727378_C_T_b38	rs890069	0.4500	-0.03	-0.75	Brain – Nucleus accumbens (basal ganglia)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.3000	-0.05	-1.00	Brain – Putamen (basal ganglia)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0810	-0.15	-1.80	Brain – Spinal cord (cervical c-1)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.1400	-0.12	-1.50	Brain – Substantia nigra
TRIB2	chr2_12727378_C_T_b38	rs890069	9.00E-07	-0.18	-5.00	Breast – Mammary Tissue
TRIB2	chr2_12727378_C_T_b38	rs890069	8.00E-10	-0.11	-6.30	Cells – Cultured fibroblasts
TRIB2	chr2_12727378_C_T_b38	rs890069	0.31	-0.08	-1.00	Cells – EBV-transformed lymphocytes
TRIB2	chr2_12727378_C_T_b38	rs890069	0.016	-0.12	-2.40	Colon – Sigmoid
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0035	-0.08	-2.90	Colon – Transverse
TRIB2	chr2_12727378_C_T_b38	rs890069	0.00034	-0.10	-3.60	Esophagus – Mucosa
TRIB2	chr2_12727378_C_T_b38	rs890069	6.20E-07	-0.19	-5.10	Esophagus – Muscularis
TRIB2	chr2_12727378_C_T_b38	rs890069	7.3E-06	-0.18	-4.60	Heart – Atrial Appendage
TRIB2	chr2_12727378_C_T_b38	rs890069	5.2E-06	-0.19	-4.60	Heart – Left Ventricle
TRIB2	chr2_12727378_C_T_b38	rs890069	NaN	NaN	NaN	Kidney – Medulla
TRIB2	chr2_12727378_C_T_b38	rs890069	0.022	-0.13	-2.30	Liver
TRIB2	chr2_12727378_C_T_b38	rs890069	8.30E-07	-0.20	-5.00	Lung

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Table 6 continued. eQTL signals between SNP rs890069 and TRIB2 in multiple types of human tissues.

Gene	Variant ID	SNP	*P*-value	NES	T-statistic	Tissue
TRIB2	chr2_12727378_C_T_b38	rs890069	0.5000	-0.05	-0.67	Minor Salivary Gland
TRIB2	chr2_12727378_C_T_b38	rs890069	4.10E-05	-0.13	-4.10	Muscle – Skeletal
TRIB2	chr2_12727378_C_T_b38	rs890069	5.10E-08	-0.18	-5.50	Nerve – Tibial
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0001	-0.22	-3.90	Ovary
TRIB2	chr2_12727378_C_T_b38	rs890069	5.20E-05	-0.14	-4.10	Pancreas
TRIB2	chr2_12727378_C_T_b38	rs890069	4.00E-07	-0.22	-5.20	Pituitary
TRIB2	chr2_12727378_C_T_b38	rs890069	0.3500	-0.05	-0.93	Prostate
TRIB2	chr2_12727378_C_T_b38	rs890069	8.30E-08	-0.16	-5.50	Skin – Not Sun Exposed (Suprapubic)
TRIB2	chr2_12727378_C_T_b38	rs890069	1.1E-06	-0.15	-4.90	Skin – Sun Exposed (Lower leg)
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0260	-0.10	-2.30	Small Intestine – Terminal Ileum
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0300	-0.12	-2.20	Spleen
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0004	-0.13	-3.60	Stomach
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0002	-0.10	-3.80	Testis
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0005	-0.14	-3.50	Thyroid
TRIB2	chr2_12727378_C_T_b38	rs890069	0.4300	-0.09	-0.79	Uterus
TRIB2	chr2_12727378_C_T_b38	rs890069	0.0030	-0.32	-3.00	Vagina
TRIB2	chr2_12727378_C_T_b38	rs890069	2.50E-09	-0.10	-6.10	Whole Blood

NES – normalized effect size.

TRIB2 is one of the pseudokinase proteins in the serine/threonine kinase superfamily. These loci have been linked to some human diseases and traits in previous genome-wide association studies, such as blood components [26], body fat percentage [27], and dental caries [28]. Interestingly, a recent genome-wide association study indicated that the *TRIB2* gene was related to optic cup area measurement [29]. This measurement describes optic nerve morphology and may be related to glaucoma pathogenesis mechanisms [29]. To date, no report has been published on supporting shared genetic architecture between cataract and primary open-angle glaucoma. Our findings may shed light on the hypothesis of a genetic overlap between the 2 typical eye diseases.

CAPRIN2 is a type of RNA binding protein. Unlike TRIB2, to which very limited evidence of eye-related diseases or traits has been linked, multiple lines of evidence have linked CAPRIN2 with eye-relevant traits in model animals [15,17,30-32]. The RNA binding proteins were believed to be involved in the post-transcriptional regulation process through mediating spatio-temporal expression of key factors related to the cell cycle [33]. This locus has been connected to some human diseases and traits in previous genome-wide association studies, including of body height [34] and waist-hip ratio [34]. What is more interesting is that these loci were found to be linked with facial morphology in a recent genome-wide association study [35]. The facial feature of the vertical position of the orbits relative to the midface was found to be strongly correlated with genetic *CAPRIN2* polymorphism [35].

For most gene association mapping scenarios, associated SNPs could be surrogates of certain underlying polymorphisms that have true effects. For the present study, although both SNPs have been reported in at least 2 independent studies, we believe that it is quite likely that both SNPs identified in the present study are just surrogates, because limited evidence has been reported for their functional consequences. Rare or low-frequency DNA variations have been demonstrated to significantly increase the susceptibility of complex diseases in a number of sequencing-based genetic studies owing to the emergence of next-generation sequencing technology [36]. A recent study indicated that 2 key eye diseases, myopia and glaucoma, might

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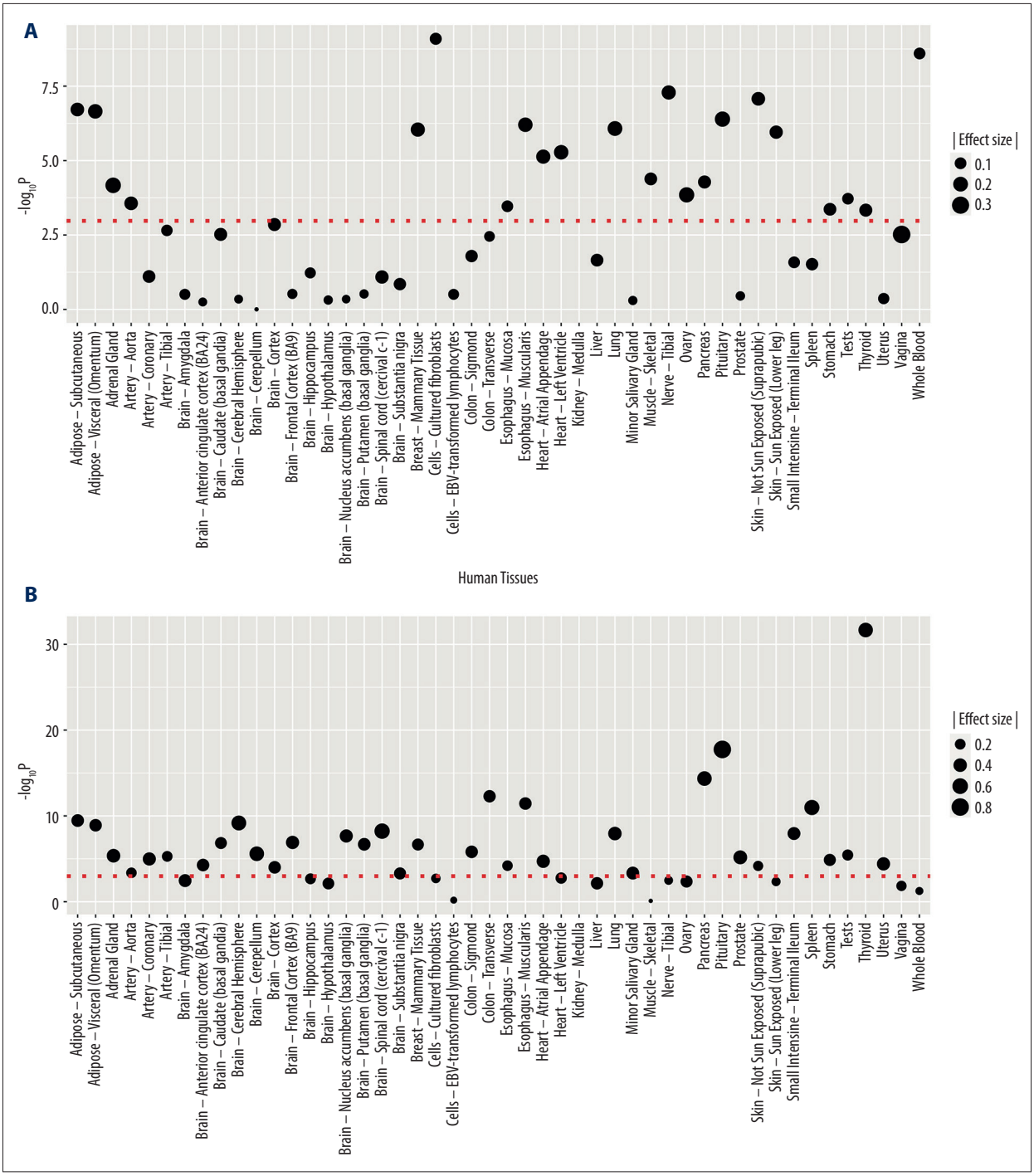

Figure 6. Expression quantitative trait loci (eQTL) signals obtained from the Genotype-Tissue Expression database. (**A**) eQTL signals for rs890069 in *TRIB2* in different types of human tissues. (**B**) eQTL signals for rs17739338 in *CAPRIN2* in different types of human tissues. Thresholds for -log *P* values are presented by dotted lines. The figure was made by R (v4.2.0) package ggplot2, manufactured by the R foundation.

primarily be influenced by rare and low-frequency DNA variants [37]. It is likely that a collection of numerous low-frequency or rare genetic variants is the source of the association signals of common genetic variants. Examining how low-frequency or rare variations on the genetic level contribute to cataract risk is outside the scope of the current investigation. Genetic research based on sequencing will be required in the future to detect the genetic characteristics of cataracts.

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Table 7. eQTL signals between SNP rs17739338 and CAPRIN2 in multiple types of human tissues.

Gene	Variant ID	SNP	*P*-value	NES	T-statistic	Tissue
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	3.40E-10	-0.33	-6.4	Adipose – Subcutaneous
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.20E-09	-0.32	-6.2	Adipose – Visceral (Omentum)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	4.2E-06	-0.41	-4.7	Adrenal Gland
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	4.20E-04	-0.19	-3.6	Artery – Aorta
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.00E-05	-0.37	-4.5	Artery – Coronary
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	5.1E-06	-0.2	-4.6	Artery – Tibial
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0034	-0.35	-3	Brain – Amygdala
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	5.20E-05	-0.32	-4.2	Brain – Anterior cingulate cortex (BA24)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.40E-07	-0.28	-5.5	Brain – Caudate (basal ganglia)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	6.50E-10	-0.52	-6.7	Brain – Cerebellar Hemisphere
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	2.5E-06	-0.5	-4.9	Brain – Cerebellum
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	9.60E-05	-0.32	-4	Brain – Cortex
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.20E-07	-0.38	-5.6	Brain – Frontal Cortex (BA9)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0021	-0.21	-3.1	Brain – Hippocampus
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0073	-0.27	-2.7	Brain – Hypothalamus
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	2.10E-08	-0.37	-5.9	Brain – Nucleus accumbens (basal ganglia)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	2.00E-07	-0.33	-5.5	Brain – Putamen (basal ganglia)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	5.70E-09	-0.57	-6.4	Brain – Spinal cord (cervical c-1)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0005	-0.29	-3.6	Brain – Substantia nigra
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	2.10E-07	-0.28	-5.3	Breast – Mammary Tissue
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0019	-0.14	-3.1	Cells – Cultured fibroblasts
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.6500	-0.047	-0.46	Cells – EBV-transformed lymphocytes
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.5E-06	-0.32	-4.9	Colon – Sigmoid
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	5.00E-13	-0.31	-7.6	Colon – Transverse
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	6.20E-05	-0.19	-4	Esophagus – Mucosa
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	3.50E-12	-0.32	-7.2	Esophagus – Muscularis
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.90E-05	-0.38	-4.4	Heart – Atrial Appendage
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0017	-0.24	-3.2	Heart – Left Ventricle
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	NaN	NaN	NaN	Kidney – Medulla

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Table 7 continued. eQTL signals between SNP rs17739338 and CAPRIN2 in multiple types of human tissues.

Gene	Variant ID	SNP	*P*-value	NES	T-statistic	Tissue
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0070	-0.31	-2.7	Liver
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.10E-08	-0.4	-5.8	Lung
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0005	-0.35	-3.6	Minor Salivary Gland
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.7900	0.014	0.27	Muscle – Skeletal
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0032	-0.11	-3	Nerve – Tibial
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0043	-0.29	-2.9	Ovary
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	4.30E-15	-0.49	-8.4	Pancreas
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.70E-18	-0.81	-9.7	Pituitary
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	6.5E-06	-0.43	-4.6	Prostate
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	6.60E-05	-0.17	-4	Skin – Not Sun Exposed (Suprapubic)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0045	-0.12	-2.9	Skin – Sun Exposed (Lower leg)
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.10E-08	-0.35	-6.1	Small Intestine – Terminal Ileum
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.00E-11	-0.55	-7.3	Spleen
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	1.30E-05	-0.29	-4.4	Stomach
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	3.5E-06	-0.22	-4.7	Testis
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	2.10E-32	-0.49	-13	Thyroid
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	3.80E-05	-0.38	-4.3	Uterus
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0140	-0.18	-2.5	Vagina
CAPRIN2	chr12_30731158_C_T_b38	rs17739338	0.0550	-0.076	-1.9	Whole Blood

NES – normalized effect size.

Table 8. Fold change of the gene expression levels in lens of mouse during the eye development process.

Gene	E10.5	E11.5	E12.5	E16.5	E17.5	E19.5	P0	P2	P28	P56
Caprin2	4.88	6.22	12.25	17.08	19.9	14.1	19.61	14.68	11.89	10.25
Trib2	-4.93	-7.02	-8.86	-5.27	-6.77	-4.35	-8.17	-3.24	-5.66	-9.29

All of the fold changes are significant.

With the rapid development of omics technology, future analysis integrating multi-omics data is expected to elucidate the molecular mechanisms of complex diseases on the basis of understanding multidimensional molecular interactions [38-43]. Therefore, it is worth mentioning some limitations of our study. The selected SNPs only cover the gene region of candidate loci. Neither 3' nor 5' untranslated regions were included. This SNP selection strategy might raise concern for the genetic information coverage of the present study because both untranslated regions have been proven to be important genomic regions containing regulatory elements for genes. Myopic individuals were included in this study, which may make it difficult to generalize the findings. A comparison of the magnitude of the risk for cataracts conferred by these gene variants in patients with high myopia versus patients without high myopia might enable us to identify noteworthy discoveries in the future.

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Conclusions

In summary, our study showed that both *TRIB2* and *CAPRIN2* conferred genetic susceptibility to cataracts in patients with high myopia with Chinese Han ancestry, offering new targets or indicators for the prevention and treatment of HMC and aiding in deepening our understanding of the genetic roots of the illness. Future research is still required to fully understand the pathogenic mechanisms and genetic characteristics of cataracts.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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