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Original Research

Association of 10 Genetic Variations and 10 Environmental Factors with Myopia of Different Severities in Different Age Groups of People in Northeast China

Yan Sun[1,2,3], Zhuang Li[2], Zhuoshi Wang[3], Xingru He[3], Sile Yu[3], Lan Hu[2], Ling Xu[2,3,*], Wei He[1,2,3,*]

[1]Department of Graduate School, Dalian Medical University, 116044 Dalian, Liaoning, China
[2]Department of Pediatric Ophthalmology, Shenyang He Eye Specialist Hospital, 110034 Shenyang, Liaoning, China
[3]Department of Artificial Intelligence, He University, 110163 Shenyang, Liaoning, China
*Correspondence: xuling@hsyk.com.cn (Ling Xu); hewei@hsyk.com.cn (Wei He)
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Abstract

Background: To investigate the association of 10 genetic variations and 10 environmental factors with myopia of different severities in different age groups of children and adolescents in northeast China. **Methods**: Parental history and genetic testing for myopia-related susceptibility genes were carried out in a cohort of children and adolescents aged 2–17 years. In addition, 10 single nucleotide polymorphism (SNP) sites for genotyping and 10 environmental risk factors were selected, and the differences between site variation and environmental factors in different age groups with different degrees of myopia were explored. **Results**: A total of 2497 volunteers were recruited, including 2023 myopes and 474 non-myopes in the control group. From the cohort, 1160 subjects were sequenced for myopia SNP sites. Compared with the non-myopic group, the myopia of parents, outdoor activity less than 60 min per day, and a high-sugar diet were risk factors for developing myopia. Two syntrophin beta 1 (*SNTB1*) sites, rs4455882 and rs6469937 were found to be significantly associated with moderate myopia; fibroblast growth factor 10 (*FGF10*) rs339501 was significantly correlated with high myopia; and insulin-like growth factor 1 (*IGF1*) rs5742714 was significantly correlated with different degrees of myopia in the age group of <6 years. Finally, the *FGF10* gene rs339501 SNP was significantly associated with moderate myopia and mild myopia in the 6- to 12-year-old age group. **Conclusions**: Our results indicate that myopia is affected by both environmental and genetic factors. To prevent and control myopia, attention should be paid to the parental history of myopia, a high-sugar diet should be avoided, and outdoor time should be adjusted according to the average daily sunshine. In addition, it is necessary to pay attention to the increased risk of myopia in school-age children caused by *SNTB1* rs4455882, *FGF10* rs339501, and *IGF1* rs5742714.

Keywords: myopia; genes; environment; single nucleotide polymorphism

1. Introduction

Myopia is one of the most common disorders of the eye, affecting a large proportion of people worldwide. The prevalence of myopia in Asian countries such as China, Japan, and Singapore is over 80% which rising rapidly over the past few decades [1–5]. In southern China, the prevalence of myopia among 13-year-old children who graduate from primary school is 36.8%, whereas the prevalence of myopia among adolescents who graduate from high school at the age of 17 has reached 53.9% [3]. It is important to note that as the degree of myopia increases, it can lead to high myopia, which in turn can increase the risk of serious ocular complications [6–8]. Therefore, it is necessary to identify children at high risk of myopia early, reduce near-work time, and increase outdoor activity time to prevent the development of myopia, thus improving general eye health [9,10].

In recent years, the pathogenesis of myopia has mainly focused on the results of the combined effect of environmental and genetic factors [1–5,11–14]. A growing number of studies has shown that environmental factors have become important risk factors for myopia in children, and the impact is further exacerbated when interacting with genetic factors. Furthermore, genome-wide association studies (GWAS) have also greatly improved our understanding of the genetic basis of myopia. Nevertheless, the same environmental risk factors have different effects on myopia risk in different regions. GWAS are also population-specific, and studies of different populations have shown different data leading to different conclusions. For example, catenin delta 2 (*CTNND2*) [15] and fibroblast growth factor 10 (*FGF10*) [16,17] are associated with different levels of risk and disease severity, suggesting that there may be complex interactions between different gene variants and the environment in East Asian populations. However, the specific genetic polymorphisms remain largely unknown [11,12]. Numerous studies have also confirmed that the effects of myopia-related locus variation vary with increasing myopia severity and age [13,14]. This suggests that some

environmental and genetic factors may play different roles in the development of myopia and its progression, and in the development of myopia in children and adolescents of different ages.

In summary, it is necessary to comprehensively analyze the multiple environmental factors of the myopic population, and at the same time conduct a multifactor analysis based on the genetic test results. This is essential to understanding the association between environmental and genetic factors, and is very helpful for understanding the development of myopia, which can be influenced by both factors. Therefore, we conducted a comprehensive study of cross-sectional environmental and genetic factors to evaluate the frequency of single nucleotide polymorphism (SNP) variant associations and interactions with myopia at multiple environmental factors and multiple loci in children and adolescents in northeast China.

2. Materials and Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki. This research proposal was approved by the Academic Committee and Ethics Committee of He Eye Specialist Hospital in Shengyang (Shengyang city, China) (IRB(2021)K007.01). Informed consent was obtained from the subject's parents or guardian.

2.1 Participants

Using a cross-sectional design, this study screened myopia subjects in a group of children and adolescents aged 2–17 years from 12 schools and kindergartens. People who had myopia attended the refractive clinic of He Eye Specialist Hospital in 21 counties, municipalities, and autonomous regions of Liaoning Province in China between October 2019 and October 2021. The inclusion criterion for myopia was children and adolescents with refraction under cycloplegia and spherical equivalent refraction (SER) below 0.50 D. Exclusion criteria were: (1) non-simple myopia, including related diseases or syndromes with myopia clinical phenotypes such as Marfan syndrome and Stickler; (2) myopia caused by lens-related diseases such as cataracts, lens dislocation, and lens congenital malformation; (3) people with other eye diseases including astigmatism, amblyopia, and corneal conjunctival and fundus diseases; and (4) those with a history of allergy to mydriatic eye drops.

In this study, the right eye was considered the standard eye. Three measurements of average objective refraction were taken from both eyes using the TOPCON300 Computerized Lensmeter (Tokyo, Japan), and subjective refraction was measured using the NIDEK COS-5100 Compact Refraction System (Tokyo, Japan). A total of 73,395 myopia subjects were screened, of whom 2497 were selected to be part of the study cohort including 1320 males and 1177 females. Subjects were divided into the following four groups according to the SER of the right eye: normal (SER $>$ –0.5 D; n = 480), low myopia (–0.5 D $\geq$ SER $>$ –3.0 D; n = 1192), moderate myopia (–3.0 D $\geq$ SER $>$ –6.0 D; n = 297), and high myopia (–6.0 D $\geq$ SER; n = 54) groups. In the study cohort, 308 participants were younger than 6 years old, 1990 were in the 6- to 12-year-old age group, and 60 were older than 12 years of age. Data on environmental factors such as sex, family history, high-sugar diet, high-fat diet, high-sodium diet, frequency of weekly outdoor activity and outdoor activity time, duration of close-range tasks, eye habits, nighttime lighting and sleeping time of the target population were collected by professional ophthalmologists, and comprehensive ophthalmic examinations were carried out using instruments and equipment of the same specifications and models including ciliary muscle paralysis (mydriasis) post-refraction, best-corrected visual acuity, intraocular pressure, slit lamp examination, fundus photography, and other physical examinations.

2.2 Selection and Genotyping of SNP

In line with previous GWAS in China, we screened 10 high-frequency susceptibility sites with high myopia in a Chinese population [18–25], including vasoactive intestinal peptide receptor 2 (*VIPR2*) rs2730260, zinc finger E-box binding homeobox 2 (*ZEB2*) rs13382811, Catenin Delta 2 (*CTNND2)* rs6885224, fibroblast growth factor-10 (*FGF10)* rs339501, insulin-like growth factor 1 (*IGF1*) rs5742714, crystallin beta A4 (*CRYBA4*) rs2009066, syntrophin beta 14 (*SNTB14*) rs4455882, syntrophin beta 16 (*SNTB16*) rs6469937, mitochondrial intermediate peptidase (*MIPEP*) rs9318086, and lumican (*LUM*) rs7308752. These gene variant loci are highly correlated with myopia in Chinese populations, and the mutation frequency is very high. Oral mucosal cells were collected from subjects by throat swab, followed by digestion with cell lysate and protease K. Then the proteins were precipitated with 5 mol/L NaCl and the DNA was precipitated with isopropanol. The obtained DNA was washed with 70% ethanol and dissolved in Tris-EDTA buffer (10 mmol/L Tris-HCl, 1 mmol/L EDTA, pH 8.0), and the SNPs were genotyped by Sanger DNA sequencing. In previous studies, these 10 SNPs were shown to positively correlate with myopia. In this study, the DNA of 1160 subjects was sequenced for the SNP sites of myopia-related genes.

2.3 Statistical Analyses

This study analyzed the frequency distribution of alleles at 10 SNP loci of the different age groups, and the differences in the results of 10 environmental factors in the normal, low myopia, moderate myopia, and high myopia groups. The main focus was to explore the correlation between associated susceptibility gene variation and environmental risk factors and different degrees of myopia. All data were statistically analyzed using Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA), and Pearson's correlation coefficient was used to

Table 1. Characteristics of the study subjects.

Group	No myopia	Mild myopia	Moderate myopia	High myopia
Definition	−0.5 D < SE < 1.0 D	−3.0 D < SE < −0.5 D	−6.0 D < SE < −3.0 D	SE <−6.0 D
Sample size (%)	23.73	58.92	14.68	2.67
Sex (female/male)	245/229	598/529	136/138	25/24
Age (mean ± SD, years)	8.76 ± 2.06	8.82 ± 1.96	8.97 ± 2.10	8.51 ± 1.74
SE (mean ± SD, D)	0.08 ± 0.32	−1.65 ± 0.61	−3.90 ± 0.80	−7.00 ± 0.72

SD, Standard deviation; SE, Spherical equivalent.

analyze sex differences. The *t*-test was used to analyze age and sex differences. Multiple inheritance models were used in the analysis of genotype data to assess each risk allele, including additive, dominant, and recessive models. *p*-values and odds ratios (ORs) in genotypic models were adjusted for age and sex. When confounding factors were adjusted, a multivariable logistic regression analysis was conducted with the degree of myopia as dependent variable and, as independent variables, 10 genetic variations and 10 environmental factors, which were significantly associated with myopia. Odds ratios (OR) and 95% (CI) were calculated to evaluate the correlation between myopia degree and environmental factors and SNP in different age groups. Bonferroni correction was applied to multiple comparisons and the significance level, alpha, was set to 0.05. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Demographic Analyses

The screening sampling rate of this study was 3.4%. The subjects were grouped according to the SER of the right eye. The normal group accounted for 23.73%, with an average age of 8.76 ± 2.06 years; the low myopia group accounted for 58.92%, with an average age of 8.82 ± 1.96 years; the moderate myopia group accounted for 14.68%, with an average age of 8.97 ± 2.10 years; and the high myopia group accounted for 2.67%, with an average age of 8.51 ± 1.74 years. The age profile of the cohort was as follows: 13% were younger than 6 years old, 85% were 6–12 years old, and 2% were older than 12 years old. There were no significant differences in age and sex between the different myopia groups ($p = 0.21$ and $p = 0.14$, respectively) (see Table 1 for more details).

3.2 Correlation Analysis of SNPs and Myopia

All 10 SNP loci were genotyped. The proportion of mutations detected at gene loci, to wit: the number of people with genetic mutations/total number of people got genetic testing from high to low were as follows: *CRYBA4* (77%), *MIPEP* (71.93%), *CTNND2* (67.47%), syntrophin beta 1 (*SNTB1*) (60.69%), *LUM* (53.99%), *VIPR2* (49.44%), *IGF1* (44.03%), *ZEB2* (41.37%), and *FGF10* (21.12%). The specific allele frequency distribution correlated with the degree of myopia (Table 2). This study found that *SNTB1* rs4455882/rs6469937 (OR: 1.626/1.658, 95% CI: 1.020–2.591/1.052–2.611) was significantly correlated with moderate myopia, whereas the other SNP loci and myopia were not significantly correlated.

The frequency of genetic SNP locus variation in myopic children and adolescents of different ages was different. *FGF10* rs339501 (OR: 1.718, 95% CI: 1.374–2.151; $p = 0.011$) was significantly correlated with high myopia in the <6-year-old age group, whereas it was significantly associated with moderate myopia (OR: 1.351, 95% CI: 1.244–1.462; $p = 0.021$) and mild myopia (OR: 1.160, 95% CI: 1.115–1.208; $p = 0.027$) in the 6- to 12-year-old age group, but was not associated with high myopia. Moreover, we found that *IGF1* rs5742714 was significantly correlated with different degrees of myopia in the <6-year-old group (OR: 1.120, 95% CI: 1.067–1.175; $p = 0.017$) (see Tables 3,4).

3.3 Correlation Analyses between Environmental Risk Factors and Myopia

The following environmental risk factors were assessed in the myopic and non-myopic group. Both parents having myopia (OR: 2.045, 95% CI: 1.033–4.049; $p < 0.001$), daily outdoor activity time less than 60 min (OR: 1.574, 95% CI: 1.090–2.119; $p < 0.001$), and continuous close-range visual tasks more than 30 min (OR: 1.094, 95% CI: 1.054–1.136; $p = 0.034$) were found to be risk factors for myopia. By contrast, outdoor activities 1–2 times per week (OR: 0.285, 95% CI: 0.123–0.659; $p = 0.079$), table lamps illuminating the eyes at night (OR: 0.431, 95% CI: 0.209–0.893; $p = 0.193$) and 8–9 h of sleep (OR: 0.260, 95% CI: 0.11–0.609; $p = 0.243$) were protective factors for myopia. The protective effect against myopia appeared to increase with an increased number of outdoor activities (≥3 times) (OR: 0.418, 95% CI: 0.182–0.960; $p = 0.395$). In addition to the above factors, a high-sodium diet (OR: 2.976, 95% CI: 1.335–6.223; $p = 0.024$) and close-range visual tasks <33 cm were additional risk factors for moderate myopia (OR: 2.41, 95% CI: 1.047–5.525; $p = 0.036$) (Table 5).

Across the different age groups, we found that a high-glucose diet (OR: 3.400, 95% CI: 1.628–7.101; $p < 0.001$) and a high-sodium diet (OR: 6.757, 95% CI: 1.764–25.641; $p = 0.021$) were additional risk factors for moderate myopia in children younger than 6 years. However, in adolescents aged 6–12 years, a high-sugar diet was a risk factor for high

Table 2. Allelic association of SNPs with different severities of myopia.

Genotypes of corresponding sites			Myopia (n = 1543) versus no myopia (n = 480)		High myopia (n = 54) versus no myopia (n = 480)		Moderate myopia (n = 297) versus no myopia (n = 480)		Mild myopia (n = 1192) versus no myopia (n = 480)	
SNP	Related genes	Risk allele	SE <−0.5D		SE ≤−6.0 D		−6.0 D < SE ≤ −3.0 D		−3.0 D < SE ≤ −0.5 D	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
rs9318086	*MIPEP*	AG	0.984	0.613/1.605	1.196	0.589/2.427	1.119	0.657/1.908	0.915	0.558/1.499
		AA	0.965	0.540/1.724	1.346	0.587/3.086	1.025	0.539/1.953	0.898	0.494/1.629
rs2730260	*VIPR2*	GT	0.910	0.592/1.401	0.665	0.357/1.236	0.976	0.607/1.567	0.917	0.589/1.429
		GG	0.797	0.409/1.553	0.596	0.216/1.642	0.839	0.399/1.764	0.808	0.406/1.610
rs4455882	*SNTB1*	AA	1.140	0.754/1.727	1.278	0.701/2.331	1.626	1.020/2.591	0.955	0.624/1.462
rs6469937		GG	1.229	0.818/1.845	1.621	0.892/2.941	1.658	1.052/2.611	1.029	0.678/1.563
rs13382811	*ZEB2*	CT	1.035	0.672/1.595	1.647	0.890/3.058	1.239	0.772/1.992	0.887	0.568/1.385
		TT	0.777	0.338/1.786	2.353	0.825/6.711	0.903	0.357/2.283	0.570	0.236/1.376
rs6885224	*CTNND2*	TT	0.973	0.633/1.497	1.065	0.573/1.976	1.054	0.654/1.695	0.925	0.594/1.441
rs339501	*FGF10*	TC	1.258	0.740/2.141	1.127	0.535/2.375	1.524	0.859/2.703	1.153	0.668/1.992
		CC	1.319	0.169/10.31	-	-	2.288	0.271/19.23	1.056	0.126/8.850
rs5742714	*IGF1*	GC	0.980	0.646/1.490	1.117	0.612/2.041	1.208	0.763/1.916	0.866	0.562/1.332
		CC	1.570	0.550/4.484	2.415	0.664/8.772	1.527	0.490/4.762	1.488	0.510/4.329
rs2009066	*CRYBA4*	GA	0.860	0.517/1.431	0.789	0.389/1.597	1.033	0.583/1.832	0.805	0.477/1.357
		AA	1.147	0.631/2.088	0.784	0.337/1.828	1.647	0.853/3.185	1.009	0.546/1.866
rs7308752	*LUM*	AA	1.095	0.731/1.642	1.096	0.615/1.957	1.079	0.691/1.686	1.103	0.727/1.672

95% CI, 95% confidence interval; OR, Odds ratio; SE, Spherical equivalent; SNP, Single nucleotide polymorphism; *MIPEP*, mitochondrial intermediate peptidase; *VIPR2*, Vasoactive intestinal polypeptide receptor 2; *SNTB1*, Recombinant Syntrophin Beta 1; *ZEB2*, zinc finger E-box binding homeobox 2; *CTNND2*, Catenin Delta 2; *FGF10*, fibroblast growth factor-10; *IGF1*, Insulin-like growth factor 1; *CRYBA4*, Human Beta-crystallin A4; *LUM*, Lumican.

Table 3. Allelic association of SNPs with different severities of myopia (<6 years of age).

Genotypes of corresponding sites			Myopia (n = 135) versus no myopia (n = 480)		High myopia (n = 6) versus no myopia (n = 480)		Moderate myopia (n = 33) versus no myopia (n = 480)		Mild myopia (n = 96) versus no myopia (n = 480)	
SNP	Related genes	Risk allele	SE <−0.5D		SE ≤−6.0 D		−6.0 D < SE ≤ −3.0 D		−3.0 D < SE ≤ −0.5 D	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
rs9318086	*MIPEP*	AG	1.486	0.683/3.226	1.333	0.435/4.082	1.842	0.760/4.464	1.361	0.608/3.040
		AA	1.258	0.467/3.390	0.857	0.188/3.922	1.305	0.419/4.065	1.302	0.468/3.623
rs2730260	*VIPR2*	GT	0.662	0.321/1.368	0.37	0.126/1.089	0.813	0.361/1.832	0.653	0.309/1.379
		GG	0.793	0.247/2.545	0.417	0.067/2.597	1.28	0.364/4.054	0.657	0.195/2.222
rs4455882	*SNTB1*	AA	1.391	0.692/2.793	1.227	0.445/3.378	2.262	1.005/5.102	1.143	0.557/2.347
rs6469937		GG	1.294	0.645/2.597	1.227	0.445/3.378	1.908	0.858/4.255	1.903	0.533/2.242
rs13382811	*ZEB2*	CT	1.318	0.634/2.740	2.597	0.886/7.634	1.346	0.596/3.040	1.193	0.561/2.538
		TT	2.865	0.368/3.232	1.048	1.239/2.111	3.089	0.437/3.250	1.684	0.201/4.085
rs6885224	*CTNND2*	TT	0.803	0.382/1.686	1.058	0.359/3.115	0.873	0.383/1.992	0.742	0.345/1.592
rs339501	*FGF10*	TC	2.016	0.687/5.917	1.739	0.421/7.194	2.591	0.828/8.130	1.789	0.593/5.405
		CC	0.65	0.074/5.747	1.718	1.374/2.151	0.451	0.027/7.407	0.842	0.091/7.813
rs5742714	*IGF1*	GC	0.945	0.474/1.883	0.903	0.330/2.469	1.312	0.608/2.833	0.806	0.394/1.647
		CC	1.120	1.067/1.175	2.315	1.597/3.344	1.466	1.244/1.730	1.185	1.101/1.274
rs2009066	*CRYBA4*	GA	1.326	0.857/2.933	0.868	0.272/2.778	1.6	0.633/4.049	1.302	0.572/2.967
		AA	1.957	0.721/5.319	1.572	0.402/6.135	2.865	0.938/8.772	1.678	0.597/4.717
rs7308752	*LUM*	AA	1.135	0.573/2.252	0.98	0.366/2.625	1.028	0.480/2.203	1.221	0.601/2.475

95% CI, 95% confidence interval; OR, Odds ratio; SE, Spherical equivalent; SNP, Single nucleotide polymorphism; *MIPEP*, mitochondrial intermediate peptidase; *VIPR2*, Vasoactive intestinal polypeptide receptor 2; *SNTB1*, Recombinant Syntrophin Beta 1; *ZEB2*, zinc finger E-box binding homeobox 2; *CTNND2*, Catenin Delta 2; *FGF10*, fibroblast growth factor-10; *IGF1*, Insulin-like growth factor 1; *CRYBA4*, Human Beta-crystallin A4; *LUM*, Lumican.

Table 4. Allelic association of SNPs with different myopia severities (6–12 years old).

Genotypes of corresponding sites			Myopia (n = 1276) versus no myopia (n = 480)		High myopia (n = 41) versus no myopia (n = 480)		Moderate myopia (n = 229) versus No myopia (n = 480)		Mild myopia (n = 1006) versus No myopia (n = 480)	
SNP	Related genes	Risk allele	SE <−0.5D		SE ≤−6.0 D		−6.0 D < SE ≤ −3.0 D		−3.0 D < SE ≤ −0.5 D	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
rs9318086	*MIPEP*	AG	0.792	0.427/1.468	1.122	0.448/2.809	0.873	0.395/1.931	0.735	0.391/1.383
		AA	0.817	0.396/1.869	1.546	0.553/4.310	0.856	0.436/1.684	0.728	0.346/1.531
rs2730260	*VIPR2*	GT	1.089	0.634/1.869	0.907	0.421/1.949	1.101	0.610/1.988	1.109	0.637/1.931
		GG	0.797	0.353/1.802	0.708	0.209/2.398	0.648	0.255/1.645	0.887	0.384/2.049
rs4455882	*SNTB1*	AA	1.038	0.620/1.739	1.304	0.617/2.755	1.406	0.793/2.494	0.877	0.517/1.488
rs6469937		GG	1.223	0.740/2.024	1.88	0.897/3.937	1.597	0.915/2.786	1.021	0.609/1.712
rs13382811	*ZEB2*	CT	0.909	0.531/1.558	1.314	0.616/2.801	1.17	0.651/2.101	0.759	0.436/1.321
		TT	0.47	0.184/1.200	1.142	0.316/4.132	0.496	0.165/1.486	0.391	0.145/1.055
rs6885224	*CTNND2*	TT	1.074	0.633/1.821	1.074	0.505/2.288	1.16	0.646/2.079	1.033	0.601/1.783
rs339501	*FGF10*	TC	1.034	0.558/1.916	0.946	0.391/2.294	1.221	0.624/2.387	0.961	0.509/1.815
		CC	1.1	1.073/1.130	-	-	1.351	1.244/1.462	1.16	1.115/1.208
rs5742714	*IGF1*	GC	1.004	0.593/1.698	1.259	0.593/2.674	1.171	0.658/2.079	0.901	0.524/1.548
		CC	1.175	0.401/3.448	2.137	0.547/8.333	0.951	0.285/3.165	1.171	0.390/3.521
rs2009066	*CRYBA4*	GA	0.651	0.331/1.280	0.699	0.283/1.730	0.782	0.371/1.647	0.596	0.299/1.189
		AA	0.829	0.385/1.789	0.504	0.168/1.511	1.182	0.606/2.732	0.739	0.337/1.621
rs7308752	*LUM*	AA	1.086	0.657/1.795	1.164	0.570/2.381	1.112	0.641/1.931	1.063	0.635/1.783

95% CI, 95% confidence interval; OR, Odds ratio; SE, Spherical equivalent; SNP, Single nucleotide polymorphism; *MIPEP*, mitochondrial intermediate peptidase; *VIPR2*, Vasoactive intestinal polypeptide receptor 2; *SNTB1*, Recombinant Syntrophin Beta; *ZEB2*, zinc finger E-box binding homeobox 2; *CTNND2*, Catenin Delta 2; *FGF10*, fibroblast growth factor-10; *IGF1*, Insulin-like growth factor 1; *CRYBA4*, Human Beta-crystallin A4; *LUM*, Lumican.

Table 5. Characteristics of the study subjects.

Group	Variate	Number	Myopia (n = 1543) versus no myopia (n = 480)		High myopia (n = 54) versus no myopia (n = 480)		Moderate myopia (n = 297) versus no myopia (n = 480)		Mild myopia (n = 1192) versus No myopia (n = 480)	
			SE <−0.5D		SE ≤−6.0 D		−6.0 D < SE ≤ −3.0 D		−3.0 D < SE ≤ −0.5 D	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Has or does not have myopic parent(s)	Parents are not myopic (Reference)									
	One parent is myopic	710	0.620	0.350/1.099	2.174	0.956/4.950	0.552	0.285/1.068	0.549	0.301/1.000
	Both parents are myopic	689	2.045	1.033/4.049	7.784	3.425/18.182	1.541	0.738/3.215	1.898	0.947/3.802
Number of outdoor activities per week	<1 time (Reference)									
	1 to 2 times	727	0.285	0.123/0.659	0.115	0.023/0.582	0.568	0.232/1.390	0.166	0.063/0.438
	≥3 times	1144	0.418	0.182/0.960	0.183	0.036/0.931	0.828	0.333/2.058	0.205	0.079/0.534
Daily outdoor activity	≥60 min (Reference)									
	<60 min	1059	1.574	1.090/2.119	1.754	1.046/2.855	1.086	0.668/1.765	0.732	0.462/1.160
Length of close-range visual tasks	<30 min (Reference)									
	30–60 min	23	1.094	1.054/1.136	1.710	1.363/2.145	1.328	1.179/1.496	1.163	1.092/1.239
	>60 min	74	1.089	1.043/1.137	1.577	1.250/1.990	1.536	1.234/1.911	1.130	1.062/1.203
Distance of close-range visual tasks	≥33 cm (Reference)									
	<33 cm	221	1.701	0.890/1.220	0.406	0.167/0.998	2.41	1.047/5.525	1.381	0.646/2.950
Lighting at night	No table lamp (Reference)									
	Table lamp	231	0.431	0.209/0.893	0.201	0.079/0.513	0.364	0.160/0.824	0.541	0.254/1.121
Sleep duration	<8 h (Reference)									
	8–9 h	1564	0.260	0.111/0.609	0.156	0.038/0.634	0.506	0.200/1.278	0.171	0.066/0.445
	≥9 h	326	0.556	0.232/1.329	0.370	0.087/1.585	0.976	0.373/2.554	0.375	0.141/1.002
High-sugar diet	Does not eat a high-sugar diet (Reference)									
	Once	1357	0.513	0.067/3.953	0.289	0.031/2.703	0.671	0.073/6.211	0.539	0.067/4.329
	Often	498	0.496	0.061/4.000	0.357	0.036/3.546	0.714	0.073/ 6.94	0.464	0.055/3.922
High-fat diet	Does not eat a high-fat diet (Reference)									
	Once	1580	0.55	0.127/2.375	0.313	0.061/1.590	0.495	0.104/2.358	0.687	0.152/3.096
	Often	230	0.546	0.112/2.660	0.476	0.081/2.809	0.733	0.136/3.968	0.458	0.089/2.375
High-sodium diet	Does not eat a high-salt diet (Reference)									
	Once	916	1.779	0.885/3.571	1.481	0.617/3.559	2.976	1.335/6.623	1.473	0.716/3.030
	Often	537	1.179	0.589/2.364	1.000	0.406/2.463	1.845	0.822/4.149	1.012	0.492/2.083

95% CI, 95% confidence interval; OR, Odds ratio; SE, Spherical equivalent; SNP, Single nucleotide polymorphism.

Table 6. Characteristics of the study subjects (>6 years of age).

Group	Variate	Number	Myopia (n = 135) versus no myopia (n = 480)		High myopia (n = 6) versus no myopia (n = 480)		Moderate myopia (n = 33) versus No myopia (n = 480)		Mild myopia (n = 96) versus No myopia (n = 480)	
			SE <−0.5D		SE ≤−6.0D		−6.0D < SE ≤ −3.0 D		−3.0 D < SE ≤ −0.5 D	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Has or does not have not myopic parent(s)	Parents are not myopic (Reference)									
	One parent is myopic	83	0.786	0.315/1.965	3.298	0.800/13.514	0.758	0.264/2.174	0.657	0.250/1.727
	Both parents are myopic	105	2.994	1.004/8.929	12.500	2.959/52.632	2.433	0.753/7.874	2.740	0.898/8.333
Number of outdoor activities per week	<1 time (Reference)									
	1 to 2 times	72	0.412	0.113/1.496	0.179	0.017/1.848	0.960	0.243/3.788	0.160	0.031/0.827
	≥3 times	154	0.227	0.054/0.952	0.208	0.017/2.518	0.658	0.144/3.013	0.072	0.012/0.417
Daily outdoor activity	≥60 min (Reference)									
	<60 min	104	1.138	1.054/1.228	1.157	0.411/3.258	1.058	0.471/2.377	0.744	0.348/1.591
Length of close-range visual tasks	<30 min (Reference)									
	30–60 min	2	1.057	1.001/1.116	1.917	1.296/2.835	1.524	1.186/1.958	1.234	1.090/1.348
	>60 min	12	1.138	1.054/ 1.228	1.500	1.005/2.238	1.286	1.004/1.646	1.083	1.002/1.172
Distance of close-range visual tasks	≥33 cm (Reference)									
	<33 cm	18	1.080	0.357/3.268	3.333	0.806/13.70	1.250	0.351/4.464	0.796	0.254/2.488
Lighting at night	No table lamp (Reference)									
	Table lamp	15	0.648	0.216/1.946	0.539	0.134/2.619	2.000	0.560/7.146	1.359	0.441/4.191
Sleep duration	<8 h (Reference)									
	8–9 h	206	0.391	0.096/1.583	0.222	0.017/2.970	0.839	0.182/3.872	4.274	0.855/21.27
	≥9 h	26	0.277	0.054/1.415	0.255	0.024/2.742	0.400	0.069/2.309	5.051	0.813/31.25
High-sugar diet	Does not eat a high-sugar diet (Reference)									
	Once	161	1.357	0.155/11.905	0.429	0.034,5.319	4.143	2.625/6.538	1.100	0.119/10.10
	Often	48	1.285	0.130/12.658	1.000	0.072,13.889	3.400	1.628/7.101	0.920	0.087/9.708
High-fat diet	Does not eat a high-fat diet (Reference)									
	Once	186	0.562	0.070/4.525	0.354	0.033,3.759	0.427	0.048/3.831	0.768	0.088/6.667
	Often	7	0.542	0.052/5.650	0.444	0.029,6.711	0.556	0.047/6.623	0.571	0.049/6.623
High-sodium diet	Does not eat a high-salt diet (Reference)									
	Once	98	3.086	0.978/9.709	9.009	1.724,47.619	6.757	1.764/25.641	1.848	0.567/6.024
	Often	43	1.623	0.538/4.902	3.003	0.533/16.950	3.559	0.949/13.333	1.105	0.353/3.460

95% CI, 95% confidence interval; OR, Odds ratio; SE, Spherical equivalent; SNP, Single nucleotide polymorphism.

Table 7. Characteristics of the study subjects (6–12 years old).

Group	Variate	Number	Myopia (n = 1276) versus no myopia (n = 480)		High myopia (n = 41) versus no myopia (n = 480)		Moderate myopia (n = 229) versus no myopia (n = 480)		Mild myopia (n = 1006) versus no myopia (n = 480)	
			SE <−0.5D		SE ≤−6.0 D		−6.0 D < SE ≤ −3.0 D		−3.0 D < SE ≤ −0.5 D	
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Has or does not have myopic parent(s)	Parents are not myopic (Reference)									
	One parent is myopic	612	0.568	0.272/1.185	1.833	0.669/5.291	0.342	0.203/1.125	0.518	0.240/1.119
	Both parents are myopic	570	1.684	0.701/0.409	6.623	2.320/18.87	1.195	0.461/3.096	1.575	0.644/3.846
Number of outdoor activities per week	<1 (Reference)									
	1 to 2 times	633	0.213	0.069/0.654	0.079	0.008/0.757	0.368	0.111/1.219	0.150	0.043/0.518
	≥3 times	960	0.563	0.199/1.593	0.157	0.017/ 1.451	0.606	0.189/1.942	0.338	0.105/1.086
Daily outdoor activity	≥60 min (Reference)									
	<60 min	913	0.913	0.523/1.595	1.816	0.854/3.861	1.113	0.606/2.045	1.361	0.762/2.427
Length of close-range visual tasks	<30 min (Reference)									
	30–60 min	18	1.072	1.029/1.117	-	-	1.239	1.091/1.407	1.125	1.049/1.206
	>60 min	61	1.111	1.044/1.183	-	-	1.786	1.262/2.528	1.164	1.064/1.274
Distance of close-range visual tasks	≥33 cm (Reference)									
	<33 cm	198	2.331	0.849/6.410	2.237	0.688/7.246	3.704	1.206/11.364	2	0.714/5.587
Lighting at night	No table lamp (Reference)									
	Table lamp	211	3.217	1.183/8.748	10.47	2.834/38.70	3.644	1.211/10.968	2.472	0.893/6.844
Sleep duration	<8 h (Reference)									
	8–9 h	1320	0.174	0.057/0.534	0.444	0.076/2.601	0.321	0.096/1.074	0.121	0.035/0.415
	≥9 h	291	0.739	0.260/2.103	0.1	0.017/0.584	0.656	0.202/2.128	0.48	0.148/1.557
High-sugar diet	Does not eat a high-sugar diet (Reference)									
	Once	1160	1.11	1.065/1.157	1.75	1.395/2.196	1.414	1.230/1.625	1.188	1.109/1.272
	Often	432	1.113	1.038/1.193	1.900	1.240/2.911	1.321	1.101/1.586	1.214	1.069/1.379
High-fat diet	Does not eat a high-fat diet (Reference)									
	Once in a while	1355	0.536	0.069/ 4.202	0.279	0.029/2.660	0.606	0.065/5.682	0.62	0.075/5.102
	Often	208	0.539	0.061/4.808	0.458	0.041/5.076	0.959	0.090/10.204	0.389	0.041/3.717
High-sodium diet	Does not eat a high-salt diet (Reference)									
	Once	797	1.244	0.502/3.086	0.573	0.186/1.770	1.792	0.643/5.000	1.279	0.499/3.279
	Often	474	0.93	0.373/2.320	0.618	0.202/1.887	1.208	0.425/3.436	0.937	0.362/2.427

95% CI, 95% confidence interval; OR, Odds ratio; SE, Spherical equivalent; SNP, Single nucleotide polymorphism.

myopia (OR: 1.900, 95% CI: 1.240–2.911; $p < 0.01$), moderate myopia (OR: 1.321, 95% CI: 1.101–1.586; $p = 0.036$), and mild myopia (OR: 1.214, 95% CI: 1.069–1.379; $p = 0.028$). Some environmental factors showed consistent effects on myopia at different ages. For example, having two myopic parents was a risk factor for myopia in children younger than 6 years (OR: 2.994, 95% CI: 1.004–8.929; $p < 0.001$) and adolescents aged 6–12 years (OR: 6.623, 95% CI: 2.320–18.868; $p = 0.024$), especially for high myopia. Furthermore, our findings suggested that sleep duration of more than 9 h was associated with a decreased risk of high myopia (OR: 0.100, 95% CI: 0.017–0.584; $p = 0.823$) (see Tables 6,7 for details).

4. Discussion

China has a high incidence of children and adolescents with myopia [26,27], but there is still a lack of population data on myopia in northeast China. This study is the first to study the association between multiple environmental factors, multi-locus SNP variation frequencies, and the severity of myopia in the northeast China. Additionally, we have also delved into the differences in the correlation between these factors and different degrees of myopia among different age groups.

Our study found that parental myopia is a risk factor for myopia in children and adolescents of all age groups in northeast China, and is particularly strongly associated with high myopia which are similar to most studies [28,29]. By the conclusion we recommend that whether or not parents are myopic should enter the myopia screening directory of children and adolescents in the region, which is very important for their clinical assessment of myopia, especially the risk of high myopia [5,13,22].

Time and frequency of weekly outdoor activities is very beneficial in reducing the risk of myopia. Outdoor activities help the retina receive enough visible or violet light stimulation at 360–400 nm, which reduces the risk of myopia. More than 14 h of outdoor activity per week reduces the risk of myopia by one-third compared to 5 h per week [30,31]. However, time spent outdoors is not the only factor as this study found that the target group spent much less time outdoors than recommended, but also showed a reduction in the risk of myopia. One hypothesis that could explain this interesting phenomenon is that high amounts of light are reflected by the snow due to the extremely long snow season in northeast China. Northeast China is located at the highest latitude in China and has the longest snow season, lasting about 6 months per year. The reflectivity of snow to sunlight is as high as 86–95%, which is 3–4 times that of grassland and 2–3 times that of the forest [31]. As a result, ambient light in northeast China is much higher than that in other regions, which may compensate for the lack of light exposure caused by low outdoor activities [32]. A recent prospective study showed that the development of myopia could be prevented and delayed in school-age children by making up for shorter outdoor activities with higher indoor illuminance (10,000 lux) [33]. Therefore, we suggest that the outdoor activity time be adjusted flexibly according to the local average ambient light for children and adolescents in different regions to prevent and control myopia.

We found that a high-sugar diet was associated with an increased risk of high myopia among adolescents in northeast China. This environmental factor has received less attention in myopia research, but there have been some findings. Major pathogenesis mechanisms include the upregulation of matrix metalloproteinase 2, degradation of collagen fibers, and elongation of the eye axis all caused by a high-sugar diet, or participation in the acetylcholine signaling pathway through thymidine triphosphate consumption, which leads to the development of high myopia [34]. At the same time, hyperglycemia also activates the polyol pathway in the lens, leading to lens swelling and excessive hydration of the lens, increased lens curvature and induced refractive myopia, and eventually high myopia. Dietary habits in different regions are an important factor influencing sugar intake. According to National Health and Nutrition Examination Survey 2013, the consumption rate of sugar-sweetened beverages is the highest among people aged 12–19 in China, especially in economically developed regions and northern China. The energy supplying ratio of added sugar in sugar-sweetened beverages reaches 8% [35,36]. Besides, insulin resistance in children and adolescents due to overweight, particularly abdominal obesityobesity, might be another reason for association between high sugar diet and myopia. Obesogenic diets and lifestyles, led to abdominal obesity and insulin resistance. It's more likely to cause sustained elevation of blood sugar in children and adolescents, ultimately leading to myopia. Meantime, in hyperinsulinemia, the promotion of increased insulin-like growth factor-1 (IGF-1) and decreased insulin–like growth factor binding protein-3 (IGFBP-3) action in scleral fibroblasts could contribute to the axial elongation of the eye which are also associated with increased risk of myopia [37–39]. The latter in combination with the results of this study suggest that a high-sugar diet may be an important risk factor of high myopia in northeast China.

The influence of genetic factors on myopia in children and adolescents is often more severe than expected. People with high genetic risk have up to a 40-fold increased risk of myopia compared with those at low genetic risk [14]. Although the causative genes of myopia are gradually discovered, it is undeniable that a large number of susceptibility gene loci variants found by GWAS have profoundly affected the progress of myopia research. Overall, only *SNTB1* rs4455882/rs6469937 is significantly associated with moderate myopia, and other SNP sites and myopia severity are not significantly correlated. However, we further evaluated the association between 10 locus sequence variants and myopia severity in children and adolescents of different ages, and found some significant genetic associ-

ation patterns. For example, in children and adolescents younger than 6 years of age, *FGF10* rs339501 was significantly associated with high myopia, *SNTB1* rs4455882 was significantly associated with moderate myopia, and *IGF1* rs5742714 was significantly associated with different myopia severity. By contrast, *FGF10* rs339501 was significantly associated with non-high myopia in children and adolescents aged 6–12 years, but other SNP sites and myopia severity were not significantly correlated. These findings show that appropriate myopia susceptibility risk assessment protocols can be developed according to different age groups.

The protein encoded by the *SNTB1* gene is an ATP-binding cassette transporter A1 (*ABCA1*)-binding protein. This gene family consists of endocellular membrane-associated proteins associated with ion channels and signal proteins. Animal experiments have suggested that *SNTB1* is expressed in the mouse retina, retinal pigmented epithelium (RPE), and sclera with differences [40–42]. *ABCA1* plays a critical role in cholesterol metabolism, and the b1-syntrophin-*ABCA1* interactions are important for cholesterol efflux [43]. To date, however, the role of *SNTB1* in the progression of myopia is unclear. In a study on Singapore Chinese schoolchildren, higher cholesterol intake was associated with longer axial length, which is the main characteristic of myopia [44], indicating a link between *SNTB1* and the development of myopia. Several GWAS have confirmed that multiple site variants of *SNTB1* gene are significantly associated with myopia susceptibility. However, different locus variants of the *SNTB1* gene are associated with different degrees of myopia [42,45]. In this study, we confirmed that two SNPs of *SNTB1* (rs4455882 and rs6469937) were significantly associated with moderate myopia in the <6-year-old myopia population in northeast China, but not with high myopia. In the >6-year-old myopic group, there was no significant association with different degrees of myopia. This suggests that rs4455882 may be associated with rs6469937 in early myopia in children in northeast China.

IGF1 has been significantly associated with high myopia in Chinese [24,25,45]. It is an important polypeptide that plays a key role in cell proliferation, differentiation, and apoptosis [46]. *IGF1* is the major growth factor underlying the proangiogenic effects, thereby inducing pathological neovascularization. *IGF1* rs5742714 is located in the enhanced subpart of the gene, and mutations in this site may lead to the overexpression of IGF1, resulting in myopia and secondary neovascularization [47]. It also can regulate scleral proteoglycan production [48], and influence scleral remodeling and myopia development. *IGF1* is structurally and functionally related to insulin. A high glycemic load carbohydrate diet might induce permanent changes in the development and progression of refractive errors [49,50]. In addition, the autocrine/paracrine function of *IGF1* and its associated binding proteins may play a role in RPE physiology and contribute to myopia genesis. Animal models have shown that *IGF1* also plays a role in controlling eye growth. In the physiological state, the growth of the sclera and retina of the eye gradually stabilizes with the age of the individual. Therefore, we infer that the effect of *IGF1* site variation on myopia decreases with age. In our study, we also found that the location variation of the *IGF1* gene was only significantly associated with myopia in children of younger age (>6 years), but no association was found in myopia in older children (>6 years), which also supports our hypothesis.

FGF10 is an epithelial mesenchymal signaling molecule that regulates extracellular matrix-associated genes, and previous studies have associated *FGF10* gene variants with high myopia [51,52]. Hsi *et al.* [51] confirmed that the risk allele of rs339501 can increase the expression level of *FGF10* by enhancing the binding of transcription factors, thereby remodeling the extracellular matrix. Sun *et al.* [52] found that rs339501, rs2973644, and rs79002828 were significantly associated with an increased risk of high myopia in Chinese young children and found that rs339501 and rs2973644 were located in the same intron regulatory region. All of these findings add to the complexity of *FGF10* gene regulation. In this study, we found that *FGF10* rs339501 was significantly associated with high myopia in the group in the 0- to 6-year-old. In the 6- to 12-year group, *FGF10* rs339501 was significantly associated with non-high myopia. This phenomenon also suggests that the expression of *FGF10* gene under different regulatory effects may cause different clinical phenotypes. This is also one of the challenges of the GWAS when encountering complex genetic variants.

The study of myopia transcriptome provides an essential help to verify and explain the specific metabolic pathways of gene and environmental factors and myopia development. Transcription factors constitute the most important functional groups of myopia pathogenesis. It has been found that 49.55% of myopic gene expression is the target of transcription factors early growth response 1, including IGF1 and FGF10 [53]. These findings will help us explore in detail the role of transcription, cutting, modification, and expression of these genes in promoting the occurrence and development of myopia in future studies. At the same time, it also provides ideal targets and intervention ideas for many myopia treatment drugs. In addition, Donato *et al.* [54] used transcriptomic methods to clarify the role of unknown genes in the metabolic pathways of disease. This method predicts the relationship between environment and gene by detecting the level of gene transcription expression in different environments. This is also very helpful for studying the interaction of genetic and environmental factors in the development of myopia.

In this study, we compared children and adolescents of different ages and myopia degrees, and analyzed the characteristics of different environmental factors and different SNP site variation frequencies between each group. This,

to the best of our knowledge, is the first large-scale study of this type in northeastern China. At the same time, however, we should point out the limitations of this study. First, the >12-year-old group had a small sample size and some data were missing, making it impossible to carry out comparative analysis of this age group. In addition, although the 10 SNP variants included in this study were confirmed to be high-frequency sites with high myopia in Chinese, these mutations may not be representative in other populations. Furthermore, the questionnaire survey results are more inclined to the subjective judgment of patients and their families, and the research conclusions only provide reference for the prevention and control of clinical myopia. Besides, this study involves multiple confounding factors, but we have not adjusted or stratified these confounding factors, such as myopia complications, myopia prevention and control methods, other myopia gene locus variations, etc., which will affect the authenticity and accuracy of the results. Finally, this was a cross-sectional study, and it is hard to observe how different environmental factors and different SNP variants affect the development of myopia and the developmental trend of the ocular axis. It was also not possible to determine a causal relationship between myopia severity and specific environmental or SNP changes. Therefore, according to the findings of this study, conducting longitudinal cohort studies on myopia development in populations exposed to different environmental factors or specific SNP variants will help us confirm and understand the role and mutual influence of high-risk environmental factors and SNPS in myopia development, and provide a basis for clinical myopia prevention and treatment, which is the main focus of future research directions.

5. Conclusions

This study investigated the various influencing factors of myopia in children and adolescents in northeast China from multiple perspectives.

As the age and prevalence of myopia among children and adolescents worldwide increases, especially in East Asia, the prevention and control of myopia among young people has become essential. This study found that the prevalence of myopia among children and adolescents in northeast China is high, and little has been done for its prevention and control in school-age children. This study found that several factors are associated with myopia risk such as parental myopia, time spent outdoors, a high-sugar diet, performing visual tasks for distances <33 cm, the use of desk lamps at night, and sleep duration. This allowed us to effectively identify and screen individuals who are more likely to develop myopia early in a population of children and adolescents. This study also revealed that *SNTB14* rs4455882, *FGF10* rs339501, and *IGF1* rs5742714 variants may affect the risk of myopia in children and adolescents. Detecting the specific genes of this SNP variant site is conducive to establishing early screening methods for related genes for myopia in children and adolescents, helping to assess, monitor, and intervene in school-age children, guiding the clinical development of personalized myopia prevention and control, and ultimately preventing the occurrence of myopia.

Abbreviations

GWAS, genome-wide association studies; SNP, single nucleotide polymorphism; SER, spherical equivalent refraction; BCVA, best-corrected visual acuity; OR, odds ratio; CI, confidence interval.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YS and ZL conceived and designed the research study. WH and LX reviewed study protocol critically and confirmed gene/environment factors. YS and LH recruited patients, performed clinical examinations, and interpretation. YS, LH and ZSW collected the clinical samples and clinical data. ZL and YS analyzed the sequencing data. YS, ZL and LX wrote and revised the manuscript. SLY and XRH analyzed data and made statistics. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All the examinations and tests involved in this study were approved by the Ethics Committee of He Eye Specialist Hospital (IRB(2021)K007.01), following the Helsinki Declaration, and obtaining informed consent from patients and family members.

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Conflict of Interest

The authors declare no conflict of interest.

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