· Original article ·

Insulin-like growth factor-1 gene polymorphisms are not associated with high myopia: a Meta-analysis

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IGF-1 基因多态性与高度近视相关性的 Meta 分析

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摘要

目的:应用 Meta 分析探讨 IGF-1 基因 2 个多态性位点(rs6214 和 rs12423791)与高度近视易患性的关系。

方法:两名作者独立检索 PubMed、EMBASE、中国期刊全文数据库(CNKI)从建库到 2014-03-12 发表的文献,合并效应采用比值比和 95% 可信区间进行评价,Meta 分析软件运用 RevMan5. 2 和 Stata 12. 0。

结果:五篇病例对照研究进入 Meta 分析,包括病例组 2585 例,对照组 3327 例,各基因模型均显示两个位点基因多态性与高度近视易患性无显著相关性。

结论:现有证据表明,尚不能认为 IGF-1 两个位点 rs6214A/G,rs12324791G/C 基因多态性与高度近视有关联性。

关键词:基因多态性;高度近视;IGF-1 基因

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Abstract

• AIM: To investigate the association between the single nucleotide polymorphisms (SNP) (rs6214 and rs12423791) in IGF-1 and high myopia susceptibility by performing a Meta-analysis.

• METHODS: PubMed, EMBASE, and Chinese National Knowledge Infrastructure (up to March 12, 2014) were searched by two authors independently. Crude odds ratios with 95% CIs were used to assess the strength of the associations between SNP rs6214, rs12324791 and high myopia. Statistical analysis was performed using the program RevMan5. 2 software (Revman; The Cochrane Collaboration, Oxford, UK) and STATA 12. 0 software (Stata Corporation, College Station, TX, USA).

• RESULTS: Five case-control studies with involving 2585 patients with high myopia and 3327 controls were included in this Meta-analysis. No statistical evidence of significant association was found in all genetic models of rs6214A/G and rs12324791G/C.

• CONCLUSION: This Meta-analysis suggested that the rs6214A/G and rs12324791G/C mutation in the insulin-like growth factor-1 are not significantly associated with high myopia.

• KEYWORDS: polymorphism; high myopia; insulin-like growth factor-1 gene

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INTRODUCTION

Myopia is a global public health problem that causes visual impairment and blindness related complications[1]. Its extreme form, high myopia, is usually defined by the presence of an axial eye length greater than 26 mm or a refractive error of less than -6. 0 diopters (D). Patients with high myopia are more susceptible to ocular abnormalities such as glaucoma,

macular degeneration, choroidal neovascularisation, or retinal detachment, all of which can cause irreversible vision loss or even blindness[2]. High myopia leads to enormous economic and social burdens due to its increasing prevalence in the populations all over the world[3].

The insulin-like grewth factor-1 (IGF-1) gene is located on chromosome 12q23.2 and has 6 exons. The IGF-1 signaling pathway plays important roles in regulating cell proliferation, differentiation and apoptosis[4,5]. Previous animal studies showed that IGF-1 contributes to eye growth and myopia development in several species[6-9]. In addition, recent genetic studies have demonstrated the role of IGF - 1 the single nucleotide polymorphisms (SNPs) in high myopia, and the rs6214 and rs12423791 polymorphisms have been shown to be correlated with high myopia susceptibility; however, the results were inconsistent. Therefore, we performed a Meta-analysis of all eligible studies for a more precise evaluation of the associations.

MATERIALS AND METHODS

Literature Search Strategy We performed a systematic search of published studies in PubMed, EMBASE and Chinese National Knowledge Infrastructure using the following keywords: "myopia", "polymorphism" and "insulin-like growth factor-1" or "IGF-1" (last search was updated on March 12, 2014). In addition, Google Scholar was used to check the references of eligible trials to ensure that all studies were included.

Inclusion Criteria This Meta-analysis included only studies that met the following criteria: 1) a case-control or cohort design; 2) evaluation of the association between SNP rs6214 or rs12423791 and high myopia; and 3) sufficient genotype frequency in both case and control populations to estimate an odds ratio with a 95% CI.

Data Extraction Information was independently extracted by two authors (Hu MX and Liang SQ) according to the inclusion criteria listed above. Disagreements were resolved by discussion or consensus. If these two authors could not reach a consensus, another author (Tan SJ) was consulted. The following data were extracted from each study: first author's name, publication year, country, genotyping methods, numbers of cases and controls, frequency of the rs6214A/G and rs12324791G/C mutations in the cases and controls, and evidence of Hardy - Weinberg equilibrium (HWE) in the controls.

Statistical Analysis Crude odds ratios (ORs) with 95% CIs were calculated to assess the strength of the association between the rs6214 and rs12423791 IGF-1 gene polymorphisms and high myopia. The pooled ORs were calculated in four genetic models in which 2 indicates the variant allele: allelic model (2 allele *vs* 1 allele), additive model (2/2 *vs* 1/1), dominant model (1/2+2/2 *vs* 1/1), and recessive model (2/2 *vs* 1/2+1/1)[10]. Between-study heterogeneity was estimated using the Q-test and I^2 statistic, and $P<0.10$ and $I^2>50\%$ demonstrated evidence of heterogeneity[11,12]. If heterogeneity existed among the studies, the ORs were pooled using a random effects model, based on the DerSimonian and Laird method. Otherwise, a fixed effects model (Mantel-Haenszel approach) was used[13,14]. Publication bias was assessed using Begg's funnel plot and Egger's test ($P<0.05$ was considered representative of statistically significant publication bias[15,16]. All of the above statistical analyses were performed using RevMan5.2 software (Revman; The Cochrane Collaboration, Oxford, UK) and STATA 12.0 software (Stata Corporation, College Station, TX, USA).

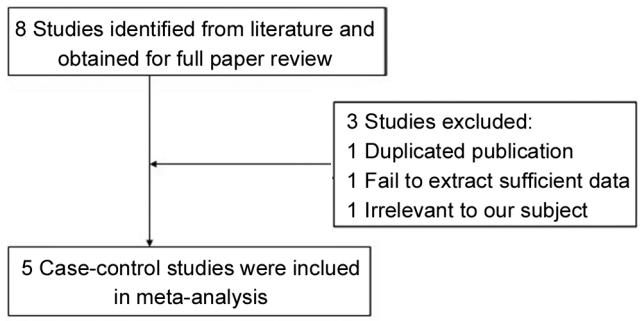

Figure 1 Flow diagram of the selection of eligible studies.

RESULTS

Study Characteristics The initial search identified 8 potentially relevant studies (Figure 1). After full-text review, three studies were excluded: one[17] was excluded because it was a duplicate publication, another[18] excluded because it was not related to high myopia and IGF-1 gene polymorphism, and the third[19] was excluded due to failure to extract sufficient data. Finally, five case-control studies, which comprised 2585 patients with high myopia and 3327 controls, were included in this Meta-analysis[20-24]. The publication years of the included papers ranged from 2010 to 2013, and all were written in English. All five studies reported an association between high myopia and the rs6214G/A polymorphism, and four of the studies addressed rs12324791G/C. We performed subgroup analyses by degree (extreme myopia). Genotyping methods included polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis, DNA sequencing and mass spectrometry (MS), and the TaqMan SNP genotyping assay. Table 1 shows the identified studies and their main characteristics. The distributions of the rs6214 and rs12324791 genotypes are presented in Table 2. All of the included studies were consistent with HWE and all genomic DNA was extracted from venous blood.

Meta-analysis Five studies were included in the SNP rs6214 G/A analysis. The Meta-analysis results are shown in Figure 2, and no evidence of a significant association was found in all of the genetic models. The combined effects were

Table 1 Main characteristics of studies included in the Meta-analysis

Study	Year	Country	Genotyping methods	Subjects (*n*)		Mean age (a)		Refractive error (D)	
				Cases	Controls	Cases	Controls	Cases	Controls
Yoshida *et al*[22]	2013	Japanese	TaqMan	446	481	37.9±11.9	39.3±11.0	-11.7±2.24	NA
Miyake *et al*[23]	2013	Japanese	TaqMan	1291	1528	57.2±14.9	50.3±15.9	-12.83±4.48	NA
Mak JY *et al*[20]	2012	Chinese	PCR-RFLP	300	300	NA	NA	-10.53±2.48	0.03±0.43
Zhuang *et al*[21]	2012	Chinese	MS	421	401	38.29±16.57	68.77±10.65	-14.57±5.60	0.39±0.82
Rydzanicz *et al*[24]	2010	Polish	PCR-RFLP	127	621	40.2±20.43	41.8±16.1	-9.69±4.0	NA

TaqMan: aqMan SNP genotyping assay; PCR-RFLP: Polymerase chain reaction restriction fragment length polymorphism; MS: DNA sequencing and mass spectrometer; NA: Data not available.

Table 2 Genetypes distribution and frequency of included studies

Study	SNP	Cases (high myopia)					Controls					Test for HWE	
		11	12	22	1	2	11	12	22	1	2	X2	*P*
Yoshida *et al*[22]	rs6214G/A				320	572				325	637	NA	
	rs12423791G/C				655	237				669	293	NA	
Miyake *et al*[23]	rs6214G/A	277	641	373	1195	1387	351	744	429	1446	1602	0.68	0.41
	rs12423791G/C	672	452	97	1796	646	835	577	108	2247	793	0.37	0.54
Mak JY *et al*[20]	rs6214G/A	80	146	74	306	294	78	137	85	293	307	2.23	0.14
	rs12423791G/C	29	132	139	190	410	30	135	135	195	405	0.197	0.66
Zhuang *et al*[21]	rs6214G/A	99	205	117	403	439	100	200	101	400	402	0.002	0.96
	rs12423791G/C	219	170	32	608	234	241	136	24	618	184	0.67	0.414
Rydzanicz *et al*[24]	rs6214G/A	51	59	17	161	93	236	307	78	779	463	2.03	0.154

HWE: Hardy-Weinberg equilibrium; NA: Data not available; SNP: Single nucleotide polymorphism.

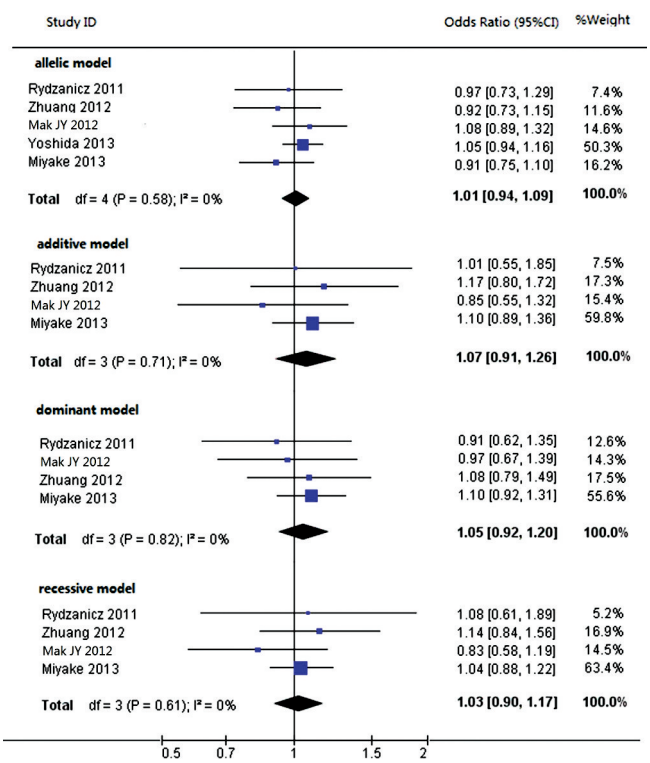

Figure 2 Forest Plot of all models for rs6214 polymorphism and high myopia The overall opposite risk was estimated with Mantel-Haenszel fixed effects model. The ORs of individual studies are shown as squares, with the size proportional to the weight of each study in the overall estimate; 95% CIs are shown as horizontal lines. The summary pooled ORs and 95 % CIs are indicated by the black diamond, respectively.

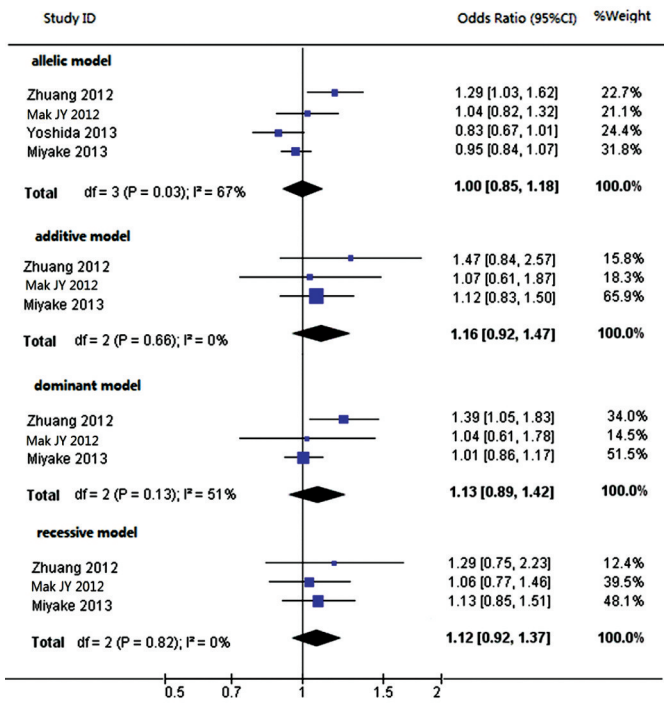

Figure 3 Forest Plot of rs12324791 polymorphism and high myopia Fixed effects models were adopted for additive model and recessive model as no significant heterogeneity was observed (I^2 = 0%, I^2 = 0%). Random effects model was used for allelic model and dominant model (I^2 = 67%, I^2 = 51%). The summary pooled ORs and 95% CIs are indicated by the black diamond, respectively.

as follows: for A allele *vs* G allele: OR = 1.01, 95% CI = 0.94, 1.09, *P* = 0.79; for AA *vs* GG: OR = 1.07, 95% CI = 0.91, 1.26, *P* = 0.43; for AA+AG *vs* GG: OR = 1.05, 95% CI = 0.92, 1.20, *P* = 0.47; and for AA *vs* AG+GG: OR = 1.03, 95% CI = 0.90, 1.17, *P* = 0.69. Regarding the association between SNP rs12324791 G/C and high myopia susceptibility, four studies were combined. There was no evidence of a significant association in any of the genetic models, too. The Meta-analysis results are shown in Figure 3.

Subgroup Analysis by Ethnicity After stratification for ethnicity, we observed that in the Caucasian population of 2458 cases and 2710 controls, there was no evidence of a significant association in any of the genetic models. Analysis of the Asian participants of 2458 cases and 2710 controls[20-24] gave results similar to those obtained with the total population. The effects about the SNP rs6214 G/A analysis of the Asian participants were as follows: for A allele *vs* G allele: OR=1.01, 95% CI=0.94, 1.10, P=0.74; for AA *vs* GG: OR=1.07, 95% CI=0.90, 1.27, P=0.42; for AA+AG *vs* GG: OR=1.07, 95% CI=0.93, 1.24, P=0.35; and for AA *vs* AG+GG: OR=1.02, 95% CI=0.90, 1.17, P=0.73.

Sensitivity Analysis We performed a sensitivity analysis to evaluate the influence of each individual study by successive omission of individual studies in every comparison. The I^2 value of heterogeneity was 0 for the heterogeneity test in the SNP rs6214 analysis. In all of the genetic models, suggesting no heterogeneity. None of the individual studies significantly affected the pooled ORs. In addition, we found that the heterogeneities of the allelic and dominant models in the SNP rs12324791 analysis were controlled by the study by Zhuang *et al*[21]. We also performed a sensitivity analysis by excluding that study, and the results did not change.

Publication Bias Publication biases were assessed using Begg's funnel plot and Egger's test quantitatively, and neither detected any obvious publication bias in the overall rs6214A/G and rs12324791G/C genetic models. The results were as follows: for the rs6214A/G mutation, P=0.299 for the allelic model, P=0.510 for the additive model, P=0.153 for the dominant model, and P=0.824 for the recessive model; for the rs12324791G/C mutation, P=0.618 for the allelic model, P=0.672 for the additive model, P=0.696 for the dominant model, and P=0.476 for the recessive model. The shapes of the funnel plots, which included all 5 studies, did not reveal any visual evidence of obvious asymmetry. Although the limited number of included trials made it difficult to interpret the publication bias results, we did not find any obvious publication biases.

DISCUSSION

The results of our Meta-analysis demonstrated that there was no evidence of significant association between the rs6214A/G or rs12324791G/C polymorphism and high myopia in the overall study population. These findings are consistent with most of the studies as included in our Meta-analyses. The greatest potential for population differentiation is likely to occur between the East Asian and the one European sample, so we performed subgroup analyses by ethnicity, no evidence of significant association was shown in any of the models for every subgroup. To investigate a more precise relationship between the rs6214A/G and rs12324791G/C polymorphism and high myopia, we performed subgroup analyses by degree of extreme myopia. However, no evidence of significant association was shown in any of the models for of the extreme myopia subgroup, either.

To better interpret the results, we should acknowledge some limitations of this Meta-analysis. Firstly, the small number of studies limits our ability to draw more solid conclusions. Secondly, some inevitablebias may exist in the results of this Meta-analysis because it only included published full text articles and may have missed some eligible studies that are unpublished. In addition, considerable heterogeneity existed among the included studies. Heterogeneity may affect the accuracy of the results despite the use of suitable Meta-analytic techniques with the random-effects model. Nonetheless, to the best of our knowledge, the present Meta-analysis is the first Meta-analysis of the relationship between the rs6214A/G polymorphism and the rs12324791G/C polymorphism and high myopia risk.

Our Meta-analysis suggests that there is no evidence of significant association between IGF-1 SNPs and high myopia. And this region was not identified in two recent large genome-wide association studies[25-26]. However, this conclusion should be considered with caution because low statistical power was determined based on the power calculations. In the future, larger sample-size studies with homogeneous populations of high myopia patients and well-matched controls are required.

In conclusion, our Meta-analysis of five case-control studies demonstrated that the rs6214 and rs12423791 SNPs in the IGF-1 gene might not be significantly associated with high myopia. Due to limitations discussed above, it is critical that larger sample-size studies with homogeneous high myopia patient populiations and well-matched controls are needed to confirm our results.

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