

A Meta-analysis of the association between different genotypes (*G11778A*, *T14484C* and *G3460A*) of Leber hereditary optic neuropathy and visual prognosis

Dong-Yu Guo, Xia-Wei Wang, Nan Hong, Yang-Shun Gu

Department of Ophthalmology, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

Correspondence to: Yang-Shun Gu. Department of Ophthalmology, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China. guyangshun_1@hotmail.com

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Abstract

• **AIM:** To analyze the influences of different genotypes (*G11778A*, *T14484C* and *G3460A*) of Leber hereditary optic neuropathy (LHON) on visual prognosis.

• **METHODS:** After a systematic literature search, all relevant studies evaluating the association between the three primary mutations of LHON and visual prognosis were included. All statistical tests were calculated with Revman 5.2 and STATA 12.0.

• **RESULTS:** Ten independent studies were included finally. A significant association between the three primary mutations and prognostic vision over 0.3 were found in *G11778A* versus *T14484C* [odds ratio (OR)=0.10, 95% confidence interval (CI)=0.05–0.17, $P<0.001$], *G11778A* versus *G3460A*(OR=0.18, 95%CI=0.09–0.37, $P<0.001$) and *T14484C* versus *G3460A* (OR=2.45, 95% CI=1.10–5.48, $P<0.05$). In addition, obtained by pairwise comparison, the vision during onset, age of onset and sex ratio of these three kinds of patients, have no statistical significance ($P>0.05$).

• **CONCLUSION:** From pairwise comparison, we conclude that these three different genotypes of LHON are related to patients' visual prognosis. The *T14484C* patients might have a best prognostic vision, *G3460A* second, and *G11778A* worst. And there is little relation between the three different genotypes and patients' vision, age of onset and sex ratio.

• **KEYWORDS:** Leber hereditary optic neuropathy; visual acuity; *G11778A*; *G3460A*; *T14484C*; Meta-analysis

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INTRODUCTION

Leber hereditary optic neuropathy (LHON) is one of the most common inherited optic neuropathies causing bilateral central vision loss [1]. LHON is the first human disease associated with a mitochondrial DNA (mtDNA) point mutation, since mtDNA mutation of *G11778A* as pathogeny of LHON was first approved by Wallace *et al* [2] in 1988. Approximately 90% of LHON pedigrees harbor one of the three primary mutations associated with the disease at mtDNA nucleotide positions *11778*, *3460*, and *14484*, all of which occur in subunits of complex I of the mitochondrial respiratory chain [3].

The clinical picture of LHON exhibits marked interpersonal variation, especially with regard to age of onset, progression rate, final visual loss and accompanying disorders [4]. Though most of people may have a slight recovery in the chronic stage, the final outcome may, however, vary from light perception to nearly complete visual recovery [5]. Therefore, it's very important to predict the prognosis of disease in the early stage. As early as 1894, Nikoskelainen *et al* [6] had reported that people with *14484* mutation might have a better visual recovery than other primary mutations. However, there is still a lack of articles with large scale to distinguish the visual outcome between these three mutations, for most of them are case report or with small sample size. Here, we performed Meta-analyses of studies on the association between the three mtDNA points' polymorphism and the clinical picture of LHON the first time in order to find out whether gene analysis could help early diagnosis and judgment for prognosis.

SUBJECTS AND METHODS

Literature Search Strategy We conducted a search for all available published studies of the association between features of onset, prognosis in patient with LHON and three primary mutations (*11778*, *14484*, *3460*) of LHON from January 1990 to July 2015: we chose "Leber hereditary optic neuropathy OR LHON", "visual acuity", "*G11778A* OR *11778* OR ND4", "*G3460A* OR *3460* OR ND1", "*T14484C* OR *14484* OR ND6" as index terms in searching databases like PubMed, Medline, Web of Science and CNKI (the largest database of science in China).

Criteria for Inclusion and Exclusion Inclusion criteria: 1) object of study: those confirmed as LHON and classified as one of the three mutations: *11778* (ND4), *14484* (ND6), *3460* (ND1); 2) observational index: it is recorded in the

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

Authors	Country	Year	¹ Vision of prognosis better than 0.3			¹ Vision of onset under 0.1		
			11778	14484	3460	11778	14484	3460
Mackey ^[7]	England	1994	1/100	20/40	4/14			
Mashima <i>et al</i> ^[8]	Japan	1998	9/124	8/16	3/8			
Mashima <i>et al</i> ^[9]	Japan	2000	1/20	4/4	2/4			
Oguchi ^[10]	Japan	2001	9/126	6/12	2/6			
Oostra <i>et al</i> ^[11]	Netherlands	1994						
Riordan-Eva <i>et al</i> ^[12]	England	1995	8/48	14/26	2/7	81/85	28/31	17/17
Wang <i>et al</i> ^[13]	China	2007				76/90	7/8	3/4
Wang <i>et al</i> ^[14]	China	2005				174/250	7/56	6/6
Wei and Sun ^[15]	China	2010	4/36	13/36		24/36	26/36	
Nikoskelainen <i>et al</i> ^[16]	Finland	1996	11/64		8/20			

¹The denominators refer to number of total cases and the numerators refer to applicable number of cases (all numbers are counted by eyes).

articles that the prognostic visions of patients (more than two) of the three mutations are over 0.3 or 0.5, while the visions are lower than 0.1 during the onset period, and the gender distribution of patients or the proportion of patients with ages of lower than 20 is also recorded, or the above values can be calculated with certain data; 3) the patients are not treated (those patients involved in treatment should not be included in the calculation); 4) as for the literatures having the same contents, the latest one should be applied. Exclusion criteria: 1) lack of primary data, the materials in four tables required for study are not available, or the relevant four table materials cannot be obtained through calculation; 2) animal study (such as rat, *etc*); 3) unavailable literatures with repeated reports, poor quality or obscure description of data used for study. The articles were reviewed independently by two investigators (Guo DY and Wang XW), who also extracted and evaluated the quality of the data. The third and fourth reviewer (Hong N and Gu YS) participated in the investigation and evaluation if there were any disagreements.

Statistical Analysis Revman 5.2 and STATA 12.0 were adopted in this study for Meta-analysis. 1) Heterogeneity test was performed for various study results, which meant to select relevant data merging method by analyzing heterogeneity among various studies through the calculation of I^2 (significant heterogeneity should be marked when $>50\%$): fixed effects model (FEM) should be adopted for data merging if there was no significant heterogeneity among various studies, or the random effects model (REM) should be adopted. 2) Calculated and evaluated the odds ratio (OR) value and its 95% confidence interval (CI) of various study results and merged data with inverse variance model and drew forest plot to demonstrate various study results and their characteristics. 3) Using the standard error of natural logarithm of OR value as x-coordinate and the natural logarithm of OR value as y-coordinate, drew the funnel plot for the description of publication bias, and then used linear regression model (Egger method) of STATA12.0 to inspect the symmetry of funnel plot, and evaluate the publication bias.

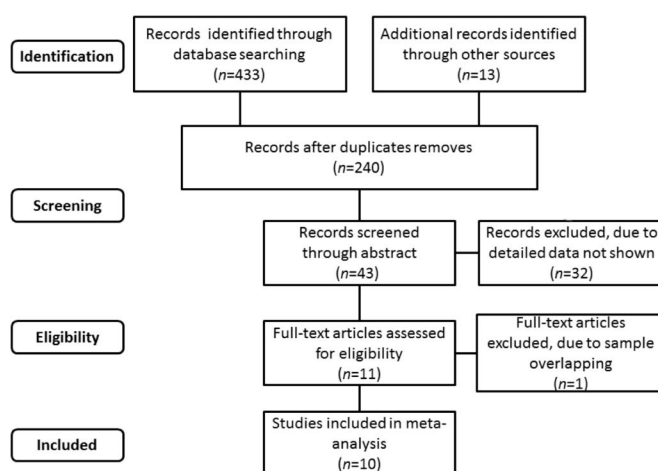


Figure 1 Flow diagram of the process of identification of eligible studies.

RESULTS

Summarized Results of Materials After the retrieval and eliminating steps taken in accordance with retrieval strategy and inclusion & exclusion criteria, 10 applicable literatures were included (all are retrospective study). The flow diagram that allowed for identification of eligible studies is illustrated in Figure 1. This article summarized 4 studies respectively: the recovery status of vision of prognosis, vision of onset, age of onset and gender proportion, and for each study, comparison between two (of three) mutation sites was performed, so the 4 studies were finally dismantled into 15 studies (the recovery status of vision of prognosis was divided into two sub-groups (vision over 0.3 and 0.5) for analysis). See Table 1^[7-16] for a summary of main basic contents of various literatures.

Heterogeneity Test of Literatures According to the results of heterogeneity tests, we discovered high heterogeneity ($I^2 > 50\%$) among three studies (Tables 2, 3), among which two are located in the studies for vision of onset, and one is located in the studies for vision of prognosis. After a careful reading of these literatures, we found that the number of cases of 3460 mutation whose vision was recovered to 0.5

Table 2 Main results obtained through Meta-analysis

Serial no.	Study project	Heterogeneity test (I^2)	Statistical model	No. of articles	No. of total cases	OR	95%CI	P
1	Vision of prognosis over 0.3 (11778 vs 14484)	48%	F	6	588	0.10	0.05, 0.17	6.7×10^{-16}
2	Vision of prognosis over 0.3 (11778 vs 3460)	16%	F	6	541	0.18	0.09, 0.37	1.2×10^{-6}
3	Vision of prognosis over 0.3 (14484 vs 3460)	0	F	5	137	2.45	1.10, 5.48	0.03
4	Vision of onset under 0.1 (11778 vs 14484)	87%	R	4	592	2.32	0.40, 13.52	0.35
5	Vision of onset under 0.1 (11778 vs 3460)	0	F	3	452	0.66	0.14, 3.10	0.60
6	Vision of onset under 0.1 (14484 vs 3460)	66%	R	3	122	0.18	0.01, 3.67	0.27

Table 3 Other results obtained through Meta-analysis

Serial no.	Study project	Heterogeneity test (I^2)	Statistical model	No. of articles	No. of total cases	OR	95%CI	P
1	Vision of prognosis over 0.5 (11778 vs 14484)	37%	F	4	447	0.13	0.07, 0.23	4.7×10^{-11}
2	Vision of prognosis over 0.5 (11778 vs 3460)	72%	R	3	230	0.11	0.00, 3.14	0.20
3	Vision of prognosis over 0.5 (14484 vs 3460)	0	F	3	171	1.84	0.39, 8.69	0.44
4	Age of onset under 20 (11778 vs 14484)	0	F	5	449	0.76	0.46, 1.24	0.27
5	Age of onset under 20 (11778 vs 3460)	0	F	5	388	0.76	0.33, 1.78	0.53
6	Age of onset under 20 (14484 vs 3460)	0	F	4	103	0.86	0.30, 2.50	0.78
7	Gender proportion of patients_male (11778 vs 14484)	47%	F	7	918	1.48	0.98, 2.24	0.06
8	Gender proportion of patients_male (11778 vs 3460)	0	F	7	649	1.81	0.83, 3.93	0.13
9	Gender proportion of patients_male (14484 vs 3460)	0	F	6	331	1.64	0.58, 4.58	0.35

and above in the sixth article (Riordan-Eva *et al*^[12]) was zero, which was the origin of heterogeneity. Since the number of patients with 3460 mutation is low and the patients whose visions are fully recovered are much lower, the number zero in this article is reasonable. What's more, the article noted down the patients date in detail, which was fully consist with our research.

We found that the resource of heterogeneity discovered in the studies for visions of onset was the seventh article (Wang *et al*^[13]) in Table 1. Since it was unable to get the detailed information of each patient in this article, we could not determine the exact reason for heterogeneity, and as a speculation, the reason was that the patients were all from Sun Yat-sen Hospital Guangzhou of China. The visions of onset of patients with 14484 mutation in Guangzhou in China were better than those of other countries and regions. However, an exclusion of this article did not cause any effects to the summarized conclusions, so we finally included it for the further summary using random effect model.

Meta-analysis Results See Tables 2, 3 for the results obtained by Meta-analysis.

From the comparisons between two (of three) mutation sites of 11778, 14484 and 3460, we concluded that the vision of prognosis of 14484 was the best (the vision of prognosis of

about 49% of patients reached 0.3 and above), followed by 3460 (about 36%), while the prognosis of 11778 was the poorest (about 8%). The results had remarkable statistical significances ($P < 0.01$, Figure 2). Although the prognosis situations of 3460 and 14484 mutation were better, there were only a small number of patients whose vision was recovered to 0.5 and above. The comparisons between two (of three) mutation sites had no advantages ($P > 0.1$), except for the comparison between 11778 and 14484 (14484 had remarkable advantage) ($P = 4.7 \times 10^{-11}$).

About the vision of onset, the comparisons between two (of three) mutation sites had no statistical significances ($P > 0.05$, Figure 3). However, from the comparisons of OR values, we could see that the vision of onset of 3460 was the poorest (about 96% lower than 0.1), followed by 11778 (about 78%), and the 14484 is the best (only 52%).

As for the age of onset of patients, the comparisons between two (of three) mutation sites had no statistical significances ($P > 0.05$). With respect to the comparisons of OR values, the age of onset of 3460 is the earliest (about 52% of patients were before 20), followed by 14484 (about 49%), and 11778 was the latest (about 44%).

As for the gender proportion of patients, the comparisons between two (of three) mutation sites had no statistical

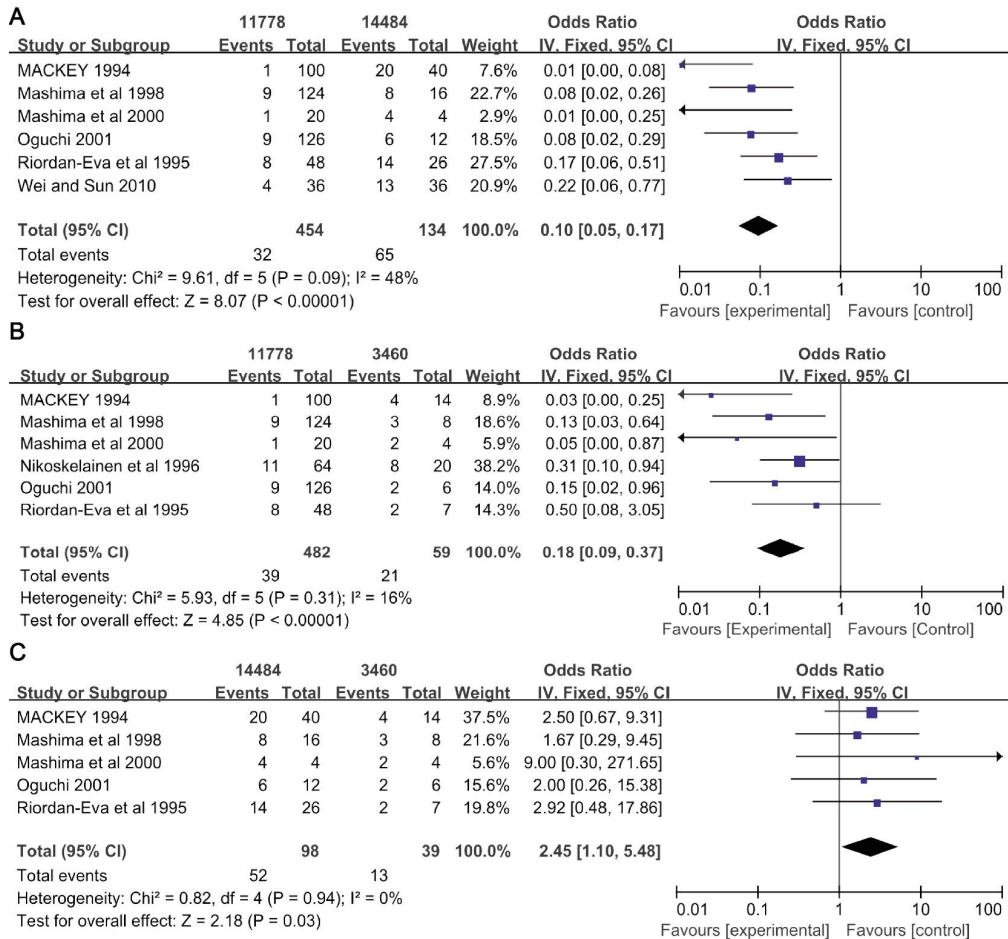


Figure 2 Forest plot of the vision of prognosis over 0.3 among the three primary mutations A: 11778 vs 14484, it shows that the prognosis of 14484 mutation in vision is remarkably better than 11778 (OR=0.10, 95%CI=0.05-0.17, P<0.001); B: 11778 vs 3460, it shows that the prognosis of 3460 mutation in vision is remarkably better than 11778 (OR=0.18, 95%CI=0.09-0.37, P<0.001); C: 14484 vs 3460, it shows that the prognosis of 14484 mutation in vision is remarkably better than 3460 (OR=2.45, 95%CI=1.10-5.48, P=0.03).

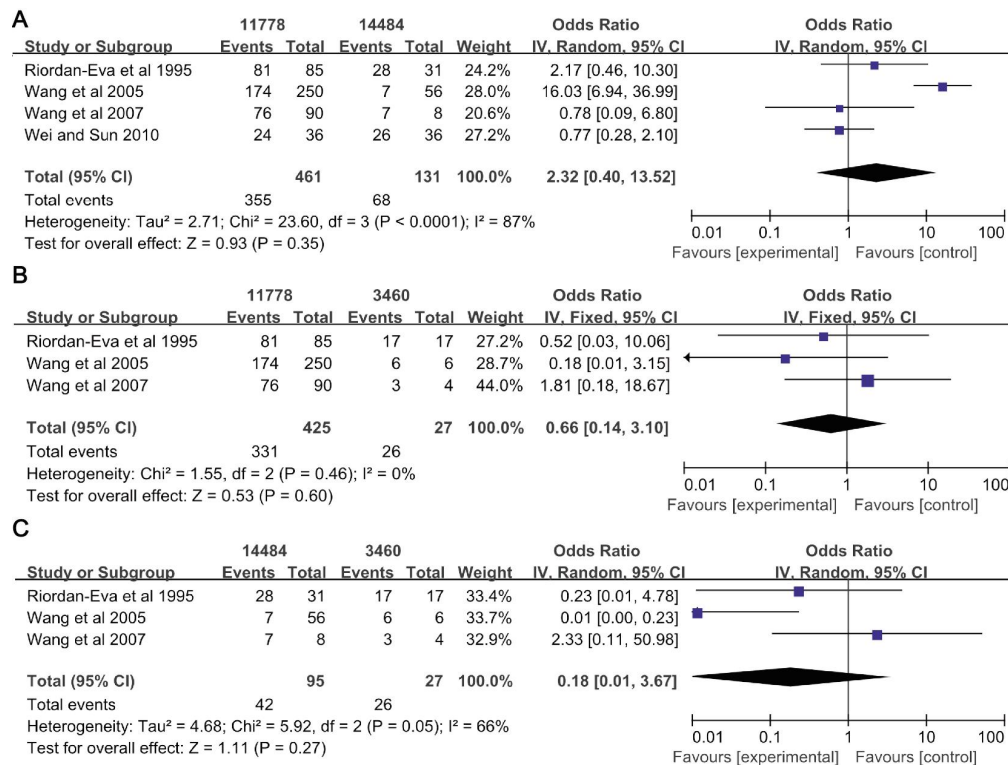


Figure 3 Forest plot of the vision of onset under 0.1 among the three primary mutations It shows no significant difference between any two of the three mutations. A: 11778 vs 14484, OR=2.32, 95%CI=0.40-13.52, P=0.35; B: 11778 vs 3460, OR=0.66, 95%CI=0.14-3.10, P=0.60; C: 14484 vs 3460, OR=0.18, 95%CI=0.01-3.67, P=0.27.

significances ($P>0.05$). From the OR value, we could see that although the male proportion of *11778* mutation was the highest and the *3460* was the lowest, the proportion was always around 80%.

Potential Publication Bias Egger algorithm of Stata 12.0 was used to inspect publication bias, and the results showed no publication bias exist except for gender proportion of patients (*11778 vs 3460*). Since the gender proportion is not the priority of this study, and the statistical results show that no specificity exists, we did not perform special processing to the gender proportion. Egger inspection cannot be performed in four of the fifteen studies because the articles are not enough, however, by drawing funnel plot with Revman 5.0, we found the points are symmetrically arranged like funnel, which proves that publication bias has little influence on Meta-analysis and the conclusion is reliable.

DISCUSSION

Most point mutations related to LHON locate in oxidative phosphorylation compounds-the element that composes NADH dehydrogenase subunit. Recently, the number of its pathogenic sites has reached more than 50^[17]. It is characterized by incomplete penetrance, as only some mutation carriers become affected^[18]. Research shows that 70%-90% LHON patients are caused by one of the three primary pathogenic sites- *G11778A*, *G3460A* and *T14484C* and its individualism can directly cause diseases^[1,5]. As LHON's clinical symptoms are relatively complex without single characteristic index and at the same time LHON can also involve the breath and movement of brain nervous system, some neurological symptoms such as cerebellar ataxia, tremor, sensory disturbance, pyramidal sign and so on^[19]. As a result, it is rather difficult to distinguish it with other optic neuropathy in clinical diagnosis. Therefore, gene screening becomes an important means to diagnose LHON.

In the aspect of the three main pathogenic sites, this research has found out that their incidence, sex ratio and age of onset in acute stage have no statistical difference. Although Sun *et al*^[20], Lai *et al*^[21] and some other researchers in China found that age of onset in patients with mutation site *14484* is little older than *11778*, our results are consist with most of the researches. Moreover, there are no differences in routine ophthalmologic examinations such as optic coherence tomography, visual evoked potential and visual field in the early stage among the three primary mutations^[22-23]. Thus, it is infeasible to distinguish the three mutations according to the early clinical symptoms and examinations. Early genetic diagnosis for those patients suspicious of LHON is very important.

In the aspect of prognosis, this research has found out that among the crowds whose prognostic vision back to 0.3 and above, mutation site *14484* has the largest proportion, *3460* second, and *11778* least. The difference between them is so tremendous that it has an outstanding statistical significance. In addition, the percent of mutation site *14484* patients

whose prognostic vision can reach 0.5 and above is 41.8%, much higher than *3460* (23.1%) and *11778* (5.9%). It is because patients with the *11778* mutation show more severe retinal nerve fiber layer (RNFL) atrophy during the late stage disease than patients with the *14484* or other mutations^[24]. What's more, Nikoskelainen *et al*^[6] and Johns *et al*^[25] have found that retinal ganglion cells in patients with *14484* mutation could reverse during the late stage. As there are no specific therapeutic methods of LHON so far^[26], early gene screening on the judgment of patients' prognosis is of great clinical significance.

In this research, we use pairwise comparison instead of network meta-analysis to find out which is better of the three and which is poorer. Although it's not statistically rigorous, there are enough data to realize pairwise comparison and it's more persuasive through direct comparison. Because there are no good standards of its prognosis ruled by guidelines or some related handbooks, different researchers apply different methods to report it. This research takes the condition of prognostic vision more than 0.3 and 0.5 as a good prognostic index to search the relevant researches and documents. Unlike Spruijt *et al*^[27], who compare the three mutations in mean value of the corresponding prognostic vision, the results will be affected if some patients' prognostic vision is quite good, even more than 1.0. Also, there are many researchers promoting certain percentage of every patient's prognostic vision as a good prognostic index to make a people counting, because of the consideration that some patients' visual loss is not quite clear in their acute onset period, which will cause the inaccuracy of prognosis. We take 0.3 and 0.5 as a good prognostic index because it can basically meet the patients' daily needs and when communicating with them, the possibility their prognostic vision being more than 0.3 or 0.5 can also be said out accurately.

In this research, we use meta-analysis for the first time to figure out whether these three primary pathogenic sites of LHON are related to patients' visual prognosis. However, there are still many deficiencies in this research. Firstly, the three genotypes contain more than 50 mutation sites such as m.3243A>G, m.8344A>G^[28-29], this research only analyzes three primary mutation sites *11778*, *14484*, *3460*, and the possibility that the primary mutation merges with secondary mutations^[30] cannot be ruled out. Secondly, the prevalence of the three mutations differs greatly that most LHON patients carry mutation site *11778*, while mutation site *3460* and *14484* are uncommon. We need to find out more data about *3460* and *14484* to increase persuasion. In addition, it is unclear whether the patients included in this research are complicated with other systemic diseases, such as multiple sclerosis^[31] or borreliosis^[32] which may have an association with LHON. What's more, since LHON's incidence is not high, the researches on large sample size clinical statistics are not many yet, more than 80% researches are case report or several families' report whose persuasion remains open to

question. Moreover, there is no good relevant standard of prognosis, while there are all kinds of reports on prognosis from different researchers, so the quantity of articles can be included at last is so limited after unification and the quality of documents is so varied, resulting in that there is not enough data to conduct a group study in detail on different races and ages of onset. Therefore, more researches still needed to draw a more persuasive conclusion.

In summary, through pairwise comparison, this research concluded the three main primary mutations has little relation with vision in acute stage, age of onset and sex ratio, but does have a relation with patients' visual prognosis. The *T14484C* patients have a best visual prognosis, *G3460A* second, and *G11778A* worst. Therefore, it is necessary to make a gene screening at early stage of LHON so as to confirm and judge prognosis.

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