Interaction of two functional genetic variants LOXL1 rs1048661 and VEGFA rs3025039 on the risk of age-related macular degeneration in Chinese women

Han Chen[1], Miao Mo[2], Guang-Yu Liu[3], Yang-Ming Gong[4], Ke-Da Yu[3], Ge-Zhi Xu[1]

[1]Department of Ophthalmology, Eye, Ear, Nose and Throat Hospital, Fudan University, Shanghai, China; [2]Department of Cancer Prevention & Clinical Statistics Center, Fudan University Shanghai Cancer Center, Shanghai, China; [3]Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; [4]Department of Cancer Control & Prevention, Shanghai Municipal Center for Disease Prevention & Control, Shanghai, China

Contributions: (I) Conception and design: KD Yu, H Chen; (II) Administrative support: KD Yu, GZ Xu; (III) Provision of study materials or patients: KD Yu, GY Liu; (IV) Collection and assembly of data: KD Yu, GY Liu, M Mo; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ke-Da Yu, MD, PhD. Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, 270 Dong An Road, Shanghai 200032, China. Email: yukeda@163.com; Ge-Zhi Xu, MD, PhD. Department of Ophthalmology, Eye, Ear, Nose and Throat Hospital, Fudan University, 83 Fenyang Road, Shanghai 200031, China. Email: xugezhi@gmail.com.

Background: Cumulative evidence indicates that LOXL1 and VEGF-a play important roles in extracellular matrix formation and angiogenesis, respectively. The disorder of extracellular matrix and angiogenesis are the key factors of pathogenesis of age-related macular degeneration (AMD). We hypothesized that rs1048661 (T>G) in the LOXL1 gene and rs3025039 (C>T) in the VEGFA gene might be associated with risk of AMD.

Methods: A total of 533 unrelated Chinese subjects, 286 cases (247 with early AMD and 39 with late neovascular AMD) and 247 controls, were included in the study. The gene sequences of LOXL1 rs1048661 and VEGFA rs3025039 were amplified by polymerase chain reaction and genotyped. Interaction between rs1048661 and rs3025039 on AMD risk was also assessed.

Results: LOXL1 rs1048661 but not VEGFA rs3025039 was associated with a significantly increased risk of AMD. The adjusted odds ratio was 1.6 (95% CI, 1.1–2.5) for rs1048661 TT + GT genotype compared with GG homozygotes in the dominant model analysis. Moreover, there was a significant gene-gene interaction between these two polymorphic loci. In VEGFA rs3025039 CC + CT genotype which indicated sufficient expression of VEGF-a, LOXL1 rs1048661 had odds ratios of 1.7 (95% CI, 1.1–2.7) for early AMD and 3.6 (95% CI, 1.1–12.3) for late neovascular AMD in the dominant model analysis. However, LOXL1 rs1048661 did not confer the risk of AMD in subjects harboring VEGFA rs3025039 TT genotype which indicated decreased expression of VEGF-a.

Conclusions: Our findings suggest that LOXL1 rs1048661 (T>G) may be involved in the risk of AMD. In addition, LOXL1 rs1048661 and VEGFA rs3025039 interacted to confer the development of AMD, especially for late-stage neovascular AMD. Our data need to be further validated.

Keywords: Single-nucleotide polymorphism (SNP); gene-gene interaction; LOXL1; VEGFA; age-related macular degeneration

Submitted Mar 12, 2020. Accepted for publication May 08, 2020.

doi: 10.21037/atm-20-2447

View this article at: http://dx.doi.org/10.21037/atm-20-2447

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision impairment and severe vision loss in the elderly (1). At present, the introduction of novel therapeutic options such as anti-vascular endothelial growth factor (VEGF) regiments provides significant clinical benefits for patients with neovascular AMD (2).

Early-stage AMD includes clinical signs such as drusen and abnormalities of the retinal pigment epithelium. Late-stage AMD could be neovascular (also known as wet or exudative) or non-neovascular (known as atrophic, dry, or non-exudative). Late AMD results in loss of central visual acuity, leading to severe and permanent visual impairment and legal blindness, which has a major impact on quality of life and functional independence.

The accurate assessment of AMD risk is of great significance to the screening and diagnosis of AMD. AMD is not only an age-associated non-genetic disease, but also a disease with probable genetic susceptibility. At least 50 genetic susceptibility loci have been identified by association and/or function studies, of which the most important variants are in the ARMS2 and CFH genes (1).

The lysine oxidase (LOX) family consists of five members in mammals, including LOX and four LOX-like proteins (LOXL1-4). They catalyze the first step in the covalent cross-linking of extracellular matrix protein collagen and elastin, which contribute to the stiffness of extracellular matrix (3). The role of LOX and LOXL2 in fibrosis and tumorigenesis has been widely studied (4). Subsequently, a genome-wide scan showed that the single-nucleotide polymorphisms (SNPs) in the LOXL1 gene were closely related to exfoliative glaucoma (5). Exfoliation syndrome is characterized by abnormal microfibril deposition that line the aqueous bathed surfaces of the anterior segment of eye. LOXL1 is a member of lysine oxidase protein, which catalyzes the oxidative deamination of lysine residues in proelastin, resulting in cross-linking with consequential formation of elastin polymer fibers. Therefore, LOXL1 may play an important role in the elastogenesis. In the pathogenesis of AMD, the degradation of age-related Bruch membrane elastic layer may lead to the formation of choroidal neovascularization (CNV). Recently, it has been reported that the elastic layer of Bruch membrane in LOXL1 deficient mice was fragmented and less continuously than in controls. These changes led to more intense CNV growth after laser photocoagulation (6).

Moreover, VEGF-a plays an important role in the regulation of angiogenesis. VEGF-a was demonstrated to be related to the formation of CNV in AMD, especially exudative AMD (7). Therefore, anti-VEGF drugs are widely used in the treatment of exudative AMD. Previous studies have shown that the genetic variants in the VEGFA gene (coding VEGF-a) may contribute to the prediction of therapeutic response to anti-VEGF drugs for AMD patients (8). However, the relationship between SNP in VEGFA and AMD risk has not been studied.

As far as we know, there is no study on the relationship between gene-gene interaction in LOXL1 and VEGFA on the risk of AMD. Here we conducted an association study to determine whether the functional polymorphisms in LOXL1 and VEGFA gene were involved in the risk of AMD in Chinese population. We selected two distinct functional polymorphisms in the LOXL1 gene (rs1048661) and the VEGFA gene (rs3025039). For rs3025039 (C>T), it was located in a predicted microRNA-binding site and had tight linkage disequilibrium (LD) with rs3025040, which could significantly interfere the miRNA-mRNA interaction and result in lower VEGF-a expression levels (9).

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2447).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Fudan University Shanghai Cancer Center of and each participant signed an informed consent document. All subjects were Chinese women, who were from a previous breast cancer screening program (10). In that program, we enrolled 14,464 women older than 35 who lived in Qibao Community, Minhang District of Shanghai, China, between May 2008 and September 2012. All these health women without history of breast cancer were screened for breast cancer by ultrasound and mammography annually. The basic demographics were recorded at the initiation of program. The blood samples were obtained and stored for genetic study. The subsequent disease events, especially breast cancer, were followed up and updated in the database. The event of breast cancer was our main interests, but we also recorded information on other diseases such as AMD during follow-up. Since AMD

were mainly occurred in mid-aged and elderly population, we only included the women aged 50 or older in the present study. In 2018, 382 women older than 50 years (at the time of enrollment) were identified to have developed to AMD which was not documented at the baseline, and 286 of them had clear records of early-stage AMD and late neovascular AMD, which two types we were interested in for the current genetic association study. The patients with late non-neovascular AMD, unknown type, or complicated pathology were excluded. The information of age, height, weight, and concomitant diseases had been recorded at the time of enrollment. Besides 286 women with AMD disease, we randomly chose additional 247 age-matched controls from the program pool.

DNA preparation

Extraction and preservation of genomic DNA, and general polymerase chain reaction (PCR) were done as previously reported (11). The DNA were extracted and stored in 2012. Genomic DNA was extracted from the leukocytes of peripheral blood and was purified with the Qiagen QIAamp Blood Kit (Qiagen, Valencia, California, USA), and the SNPs rs1048661 in the LOXL1 gene and rs3029039 in the VEGFA gene were directly sequenced and genotyped after amplification by PCR. The primers for rs1048661 were:

forward 5'-CTCAGCGCTCCGAGAGTAG-3',
reverse 5'-ACACGAAACCCTGGTCGTAG-3'.
The primers for rs3029039 were:
forward 5'-ACACCATCACCATCGACAGA-3',
reverse 5'-GGCTCGGTGATTTAGCA-3'.

The purified PCR products were sequenced on an ABI 3730 XL sequencer (Applied Biosystems, USA).

Diagnosis of AMD

The records of AMD were derived from the database and the diagnosis were further confirmed by phone-call visit. If there was an unclarity, the patient was directly recommended to the Eye Institute of Fudan University Eye and ENT Hospital for on-site diagnosis by Dr. HC or ZGX. Patients underwent a series of ophthalmic examinations, including visual acuity measurement, color fundus photography, slit-lamp microscopy of the fundi, optical coherence tomography, as well as angiography, for accurate diagnosis and classification. The type and status of the AMD was determined by the consensus of 2 retina specialists. The epidemiological classification by Wisconsin grading (12) was used. Patients were classified into early AMD [large (≥125 μm) drusen or retinal pseudo-drusen, or pigmentary abnormalities] and late AMD (neovascular AMD or geographic atrophy). The neovascular (also known as exudate) AMD subjects should have clear CNV networks with diffuse staining of CNV membranes by the angiography imaging. In the present study, we just included the women diagnosed with early-stage or late neovascular AMD, and other cases with equivocal diagnosis or late non-neovascular AMD were excluded.

Statistical analysis

The differences in genotype frequencies among the AMD cases and controls was tested by the chi-square or Fisher exact test when necessary, depending on the cell counts. Odds ratio (OR) (approximated to relative risk) was calculated as a measure of the risk of genotypes of LOXL1 rs1048661 and VEGFA rs3025039 on the phenotype of AMD using the additive model (wild/wild *vs.* wild/mutant *vs.* mutant/mutant) and dominant model (wild/wild *vs.* wild/mutant and mutant/mutant combined), respectively. The significance of single-locus association result was corrected using the Bonferroni correction. OR with 95% confidence intervals (CI) were estimated using logistic regression analysis. The Hardy-Weinberg equilibrium was tested to compare the observed genotype frequencies to the expected ones in the controls. A gene-gene interaction was evaluated by logistic regression analysis. A two-sided P value of ≤0.05 was considered statistically significant. Statistical analysis was performed using Stata software (version 13. Stata Corp LP).

Results

Distribution of LOXL1 rs1048661 and VEGFA rs3025039 genotypes in women

Table 1 shows the basic information of the cases and controls. There were 533 study subjects, 286 in the case group and 247 in the control group. The median age of the subjects was 59 years old at the time of enrollment. We noticed that comorbidity of hypertension seemed to be an important risk for the development of AMD. Of 286 AMD patients, 247 (86.4%) were diagnosed as early AMD and 39 (13.6%) with late neovascular AMD.

Both SNPs, LOXL1 rs1048661 and VEGFA rs3025039, adhered to the Hardy-Weinberg expectations in the control

Table 1 Demographic and selected variables in cases and controls

Characteristics	Controls (N=247)	AMD cases (N=286)	P
Age (median, range)	59 [50–85]	59 [50–84]	0.77
BMI (median)	24.0	25.3	0.08
Marriage, n (%)			0.64
Unmarried	22 (8.9)	22 (7.7)	
Married	212 (85.8)	244 (85.3)	
Divorced	13 (5.3)	20 (7.0)	
Diabetes, n (%)			0.71
No	184 (74.5)	209 (73.1)	
Yes	63 (25.5)	77 (26.9)	
Hypertension, n (%)			0.01
No	165 (66.8)	151 (52.8)	
Yes	82 (33.2)	135 (47.2)	
Type of AMD, n (%)			
Early-stage	NA	247 (86.4)	NA
Late neovascular	NA	39 (13.6)	

AMD, age-related macular degeneration; BMI, body mass index; NA, not applicable.

group (P>0.05). The genotype distribution of the two SNPs in the cases and controls was evaluated and showed in *Table 2*. Using the additive model, the distribution of TT and GT genotypes of rs1048661 (TT 22.0%, GT 61.2%) in the case group were higher than those in the control group (TT 15.4%, GT 59.9%), with a P value of 0.028 and Bonferroni corrected P of 0.056. In the dominant analysis model, women with the T-allele containing genotypes had an increased risk of AMD compared with GG genotype with a corrected P of 0.048. Correspondingly, the estimated OR was 1.6 (95% CI, 1.1–2.5) for AMD risk after adjustment of age, BMI, marriage status, and comorbidity. In contrast, VEGFA rs3025039 was not associated with the risk of AMD.

Interaction of LOXL1 rs1048661 and VEGFA rs3025039 on AMD risk

Then we studied the combined effect of rs1048661 and rs3025039 on AMD risk. Because previous studies had shown that the T-allele of VEGFA rs3025039 conferred a decrease in VEGF-a expression and expression levels of VEGF-a could be related to AMD risk, we here speculated that LOXL1 might affect the risk of AMD in patients with sufficient expression of VEGF-a, but not in those with inadequate concentration of VEGF-a. According to rs3025039 genotype, we divided the patients into two groups, one is TT homozygous genotype, indicating VEGF-a expression is insufficient; the other is CC+CT genotype, indicating VEGF-a concentration is relatively adequate. As shown in *Table 3*, in the low VEGF-a group (rs3025039 TT genotype), LOXL1 rs1048661 was not a modifier of AMD risk. However, in the normal or high VEGF-a expression group (rs3025039 CC+CT genotype), LOXL1 rs1048661 T allele-containing genotypes were significantly associated with early AMD (OR =1.7, 95% CI, 1.1–2.7) compared with the GG genotype, and the difference was even tremendous for exudative AMD (OR =3.6, 95% CI, 1.1–12.3). Furthermore, in the high VEGF-a expression group (rs3025039 CC homozygotes), LOXL1 rs1048661 T allele-containing genotypes were also significantly related to AMD (OR =2.1, 95% CI, 1.1–4.1, P=0.026) when compared with GG genotype.

Discussion

In the present community women-based case-control study, we investigated the association of two functional genetic polymorphisms, rs1048661 in the LOXL1 gene and rs3025039 in the VEGFA gene, with the risk of AMD in Chinese women. We found that LOXL1 rs1048661 significantly contributed to the risk of AMD. Moreover, we for the first time revealed that, LOXL1 rs1048661 and VEGFA rs3025039 interacted to confer development of AMD, especially for the type of exudative AMD. These findings support our hypothesis that potentially functional polymorphisms may play a role in the etiology of AMD, and the effect of genetic polymorphism could be mediated by the microenvironment, such as differential concentrations of VEGF-a, which is involved in the formation of choroidal neovascularization for exudative AMD.

In an earlier study, rs1048661 in the LOXL1 gene was demonstrated to be functional and was strongly associated with exfoliation glaucoma (5). The hazardous G-allele led to a reduced expression of LOXL1 by an estimated 7.7% and contributed 2.5 times of exfoliation glaucoma risk. Subsequently, other studies in Caucasian population validated the findings, with the G-allele and GG genotype

Table 2 Two polymorphisms and risk of AMD

Genotype	Controls (%)	AMD cases (%)	P	OR with 95% CI[#]	P after Bonferroni correction
LOXL1 rs1048661					
Additive model			0.028		0.056
GG	61 (24.7)	48 (16.8)		–	
GT	148 (59.9)	175 (61.2)		–	
TT	38 (15.4)	63 (22.0)		–	
Dominant model			0.024		0.048
GG	61 (24.7)	48 (16.8)		Reference	
GT + TT	186 (75.3)	238 (83.2)		1.6 (1.1–2.5)	
VEGFA rs3025039					
Additive model			0.098		1.0
CC	84 (34.0)	97 (33.9)		–	
CT	116 (47.0)	153 (53.5)		–	
TT	47 (19.0)	36 (12.6)		–	
Dominant model			0.98		1.0
CC	84 (34.0)	97 (33.9)		–	
CT + TT	163 (66.0)	189 (66.1)		–	

[#], adjusted for age, BMI, marriage status, and comorbidity. AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.

as the risk factors (13). In contrast, studies from East Asian populations, including Japanese, Chinese and Korean populations, found that the allele and genotype distributions of rs1048661 were quite different from those in Caucasian population (13). Fuse and colleagues revealed that it was the T-allele but not the G-allele that played a hazardous role for the neovascular AMD (14). Our study had similar findings to the Japanese investigation, with an estimated OR of 1.6 (95% CI, 1.1–2.5) in AMD risk for the hazardous T-allele-containing genotypes.

Microenvironmental factors could have influenced the pathways that lead to either early AMD or late AMD. As we had known, VEGF-a plays a crucial role in the maintenance of endothelial integrity and regulation of angiogenesis. Polymorphisms within VEGFA were associated with an increased risk of stroke and cardiovascular risk by regulating concentration of VEGF-a as well as leptin serum level (15). Similarly, because VEGF-a participated in the formation of choroidal neovascularization in exudative AMD, we conjectured that SNPs in VEGFA might be associated with or modified the risk of AMD. Our results did not support the single locus of VEGFA rs3025039 could increase the risk of AMD. It was consistent with the other report from the Chinese Tujia ethnic minority group (16). However, the interaction between LOXL1 rs1048661 and VEGFA rs3025039 needs to be investigated.

Both genetic/environmental factors and their interactions contribute to the risk and progression of AMD. To reveal the potential effect of gene-gene interaction, we integrally analyzed the contribution of these two SNPs to the risk of AMD. The results were interesting. In the theoretical low VEGF-a concentration group, LOXL1 rs1048661 could not modify the AMD risk. While in the normal/sufficient VEGF-a concentration group, rs1048661 is highly associated with exudative AMD, whose pathogenetic mechanism is connected to the very VEGF pathway. Our findings are biologically plausible because blood VEGF-a concentration could be affected by SNPs in the VEGFA gene, and LOXL1 might play a role in AMD risk only when the requirement of biological VEGF-a concentration is met. Our findings are consistent with the fact that VEGF-a plays an important role in the regulation of angiogenesis and it is involved in the formation of choroidal neovascularization for AMD.

Table 3 Interaction between LOXL1 rs1048661 and VEGFA rs3025039 on AMD risk

Subjects	rs3025039 CC or CT (N=450)				rs3025039 TT (N=83)		
	rs1048661 GG (N=92)	rs1048661 GT + TT (N=358)	P	OR (95% CI)	rs1048661 GG (N=16)	rs1048661 GT + TT (N=67)	P
Controls	52 (26.0%)	148 (74.0%)	0.018	Reference	9 (19.1%)	38 (80.9%)	0.54
Cases (early AMD)	37 (17.1%)	179 (82.9%)		1.7 (1.1–2.7)	6 (19.4%)	25 (80.6%)	
Cases (late, neovascular)	3 (8.8%)	31 (91.1%)		3.6 (1.1–12.3)	1 (40.0%)	4 (60.0%)	

AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.

Several limitations of our study need to be addressed. First, it lacked the measurement of VEGF-a expression levels according to genotype in the retina or blood, although another study had conducted the functional experiments in tool cell lines such as HEK293T (9). Second, the number of subjects in this study was moderate, and the statistics was underpowered in subgroup analysis. For instance, there were only 39 cases with late neovascular AMD. We believed subsequent analyses with larger sample size would provide more information, and a relevant meta-analysis might be more reliable. Third, we only chose SNPs that have been previously reported. A genome-wide study should be carried out to find more pathogenic SNPs. Finally, our study was gender-biased. Using the data from a community-based breast cancer screen program, we could only assess the AMD risk in female population and the results could be extrapolate to the male population. Therefore, the study subjects, particularly AMD cases, may not be representative for general population. Our findings need to be interpreted cautiously. Further experiments are needed to confirm this association and the associations need to be validated in other large population-based studies.

In conclusion, the genetic polymorphism LOXL1 rs1048661 is a common variant in Chinese women and is associated with risk of AMD. We also reveal a gene-gene interaction between LOXL1 and VEGFA, which contributes to the development of AMD. Further studies are needed to reconfirm our findings.

Acknowledgments

Funding: Supported by grants from the National Natural Science Foundation of China (81672600, and 81722032), 2018 Shanghai Youth Excellent Academic Leader, Fudan Zhuoshi Project, Study on comprehensive prevention and control of common eye diseases in Xuhui District (XHLHGG201807), and Shanghai Key Laboratory of Visual Impairment and Restoration.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-2447

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-2447

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-2447). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work (including full data access, integrity of the data and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Committee of Fudan University Shanghai Cancer Center of and each participant signed an informed consent document.

References

1. Mitchell P, Liew G, Gopinath B, et al. Age-related macular degeneration. Lancet 2018;392:1147-59.
2. Waugh N, Loveman E, Colquitt J, et al. Treatments for dry age-related macular degeneration and Stargardt disease: a systematic review. Health Technol Assess 2018;22:1-168.
3. Barker HE, Cox TR, Erler JT. The rationale for targeting the LOX family in cancer. Nat Rev Cancer 2012;12:540-52.
4. Iturbide A, Garcia de Herreros A, Peiro S. A new role for LOX and LOXL2 proteins in transcription regulation. FEBS J 2015;282:1768-73.
5. Thorleifsson G, Magnusson KP, Sulem P, et al. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science 2007;317:1397-400.
6. Nita M, Strzalka-Mrozik B, Grzybowski A, et al. Age-related macular degeneration and changes in the extracellular matrix. Med Sci Monit 2014;20:1003-16.
7. Ambati J, Ambati BK, Yoo SH, et al. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol 2003;48:257-93.
8. Kepez Yildiz B, Ozdek S, Ergun MA, et al. CFH Y402H and VEGF Polymorphisms and Anti-VEGF Treatment Response in Exudative Age-Related Macular Degeneration. Ophthalmic Res 2016;56:132-8.
9. Zhao J, Bai Y, Jin L, et al. A functional variant in the 3'-UTR of VEGF predicts the 90-day outcome of ischemic stroke in Chinese patients. PLoS One 2017;12:e0172709.
10. Mo M, Liu GY, Zheng Y, et al. Performance of breast cancer screening methods and modality among Chinese women: a report from a society-based breast screening program (SBSP) in Shanghai. Springerplus 2013;2:276.
11. Yu KD, Di GH, Fan L, et al. A functional polymorphism in the promoter region of GSTM1 implies a complex role for GSTM1 in breast cancer. FASEB J 2009;23:2274-87.
12. Klein R, Meuer SM, Myers CE, et al. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol 2014;21:14-23.
13. Founti P, Haidich AB, Chatzikyriakidou A, et al. Ethnicity-Based Differences in the Association of LOXL1 Polymorphisms with Pseudoexfoliation/Pseudoexfoliative Glaucoma: A Meta-Analysis. Ann Hum Genet 2015;79:431-50.
14. Fuse N, Mengkegale M, Miyazawa A, et al. Polymorphisms in ARMS2 (LOC387715) and LOXL1 genes in the Japanese with age-related macular degeneration. Am J Ophthalmol 2011;151:550-6.e1.
15. Yadav BK, Yadav R, Chang H, et al. Genetic Polymorphisms rs699947, rs1570360, and rs3025039 on the VEGF Gene Are Correlated with Extracranial Internal Carotid Artery Stenosis and Ischemic Stroke. Ann Clin Lab Sci 2017;47:144-55.
16. Liu S, Wu M, Zhang B, et al. Analysis of genetic polymorphisms for age-related macular degeneration (AMD) in Chinese Tujia ethnic minority group. BMC Med Genet 2019;20:25.

Cite this article as: Chen H, Mo M, Liu GY, Gong YM, Yu KD, Xu GZ. Interaction of two functional genetic variants LOXL1 rs1048661 and VEGFA rs3025039 on the risk of age-related macular degeneration in Chinese women. Ann Transl Med 2020;8(13):818. doi: 10.21037/atm-20-2447

