Received: 11 February 2017 | Accepted: 23 March 2017

DOI: 10.1002/jcla.22238

RESEARCH ARTICLE

WILEY

Association of the rs1760944 polymorphism in the *APEX1* base excision repair gene with risk of nasopharyngeal carcinoma in a population from an endemic area in South China

Zhifang Lu[1] | Sisi Li[1] | Sisi Ning[1] | Mengwei Yao[1] | Xunzhao Zhou[1] | Yuan Wu[1] | Changtao Zhong[1] | Kui Yan[1] | Zhengbo Wei[2] | Ying Xie[3]

[1]Graduate School of Guangxi Medical University, Nanning, China

[2]Department of Head and Neck Tumor Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China

[3]Guangxi Key Laboratory for High-Incidence Tumor Prevention and Treatment, Experimental Center of Medical Science of Guangxi Medical University, Nanning, China

Correspondence
Zhengbo Wei, Department of Head and Neck Tumor Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China.
Email: wzhbo1973@aliyun.com
and
Ying Xie, Key Laboratory for High-Incidence Tumor Prevention and Treatment, Ministry of Education and Experimental Center of Medical Science of Guangxi Medical University, Nanning, China.
Email: xieying2002@hotmail.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81360406 and 81460415; Guangxi Natural Science Foundation of China, Grant/Award Number: 2016GXNSFAA380096; Ministry of Education Key Laboratory for High-Incidence Tumor Prevention and Treatment foundation, Grant/Award Number: GKE2015-ZZ10

Background: Apurinic/apyrimidinic endonuclease 1 (APEX1) plays a central role in the repair of oxidative DNA lesions via base excision repair, and polymorphism in the *APEX1* gene may affect susceptibility to carcinogenesis.

Methods: Here, we assessed possible relationships between single-nucleotide polymorphism at *APEX1* rs1760944 and risk of nasopharyngeal carcinoma (NPC) in 477 NPC patients and 558 healthy controls from Guangxi province, which is the second largest NPC endemic area in South China.

Results: Genotype frequencies in controls were in Hardy-Weinberg equilibrium. Logistic regression analysis identified the genotypes GT or GG as associated with significantly lower risk than the genotype TT (adjusted odds ratio [OR] 0.745, 95% confidence interval [CI] 0.573-0.970). This apparent protective effect of GT/GG was even greater among those with no smoking history (adjusted OR 0.679, 95%CI 0.494-0.934).

Conclusion: Our results suggest that *APEX1* rs1760944 polymorphism may correlate with NPC susceptibility in a population from an endemic area in South China.

KEYWORDS
base excision repair, human apurinic/apyrimidinic endonuclease 1, nasopharyngeal carcinoma, single-nucleotide polymorphism

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor with high incidence and recurrence in southern China, especially in the provinces of Guangdong and Guangxi.[1] In these regions, its annual incidence is as high as 50 per 100 000,[2] and about 50% of patients, especially those with late stage experience recurrence after radical treatment,[1,3,4] suggesting that early diagnosis may decrease the recurrence risk and thus improve the outcome of NPC patients. Searching risk factors may help to identify the susceptible populations and increase the early diagnosis rate for NPC. In recent years, more and more studies reported that genomic DNA damage may be associated with NPC onset and progression,[5,6] implying that malfunction of DNA repair pathways may be a risk factor and affect the susceptibility to this cancer. Indeed, several single-nucleotide polymorphisms (SNPs), such as 1349 T>G in the fifth exon (rs1130409) and −656 T>G in the promoter region (rs1760944) in the gene encoding apurinic/apyrimidinic endonuclease 1 (APEX1),[7–10] which is a key player in the DNA base excision repair

Zhifang Lu and Sisi Li are contributed equally to this article.

pathway,[11,12] reduce the expression or activity of APEX1, and this reduction increases risk of malignant tumors.[13,14] APEX1 acts as an endonuclease and phosphodiesterase to incise at apurinic/apyrimidinic sites of oxidative base damage in DNA,[15,16] so reducing its activity should allow accumulation of DNA damage that can lead to cancer.

One of the best studied SNPs in the *APEX1* gene is rs1760944, which is associated with risk of several cancers.[7,17] Some previous studies indicated that G allele at rs1760944 may contribute to a lower risk of malignant tumors. Lo et al.[14] revealed that individuals with GT or GG genotypes would have a decreased risk of lung cancer compared with those with TT. Kang et al.'s[18] study showed that GT or GG genotypes may have a protective effect on breast cancer susceptibility. Regarding NPC, only one study was published in the literature about relation of its susceptibility to rs1760944 SNP. Working with a Chinese population from the south-central city of Chongqing (a non-endemic area of China), Li et al.[7] found that the genotype GG at rs1760944 tended to be associated with lower risk of NPC than other genotypes, suggesting that it could protect against NPC, although the data did not reach statistical significance. To our best knowledge, no related study from endemic areas has been published, and little is known about the associations of rs1760944 SNP with NPC risk in these regions.

Therefore, we examined these possible associations with a population from Guangxi province, which is the second largest endemic area of NPC in South China. We controlled sex, age, and smoking history in order to analyze associations in detail.

2 | METHODS

2.1 | Study population

This study involved patients diagnosed with NPC and treated at the Affiliated Tumor Hospital of Guangxi Medical University (Nanning, China) from July 2012 to June 2015. Over the same period, healthy controls were recruited from individuals undergoing routine physical examination at the Affiliated Tumor Hospital and the first Affiliated Hospital of Guangxi Medical University. The Ethics Committee of Guangxi Medical University approved the study, and each participant provided written informed consent at enrollment.

2.2 | Blood collection

Venous blood (3 mL) was collected from all participants into ethylenediaminetetraacetic acid-containing tubes. Genomic DNA was extracted using the TGuide Blood Genomic DNA Kit (Tiangen, Beijing, China) according to the manufacturer's instructions. Purity and quality of DNA samples were assessed using the ratio of absorbance at 260 and 280 nm as well as agarose gel electrophoresis.

2.3 | Genotyping

Target fragments were amplified using the polymerase chain reaction (PCR) and primers designed with MassARRAY Assay Design Version 3.1 software (Sequenom, San Diego, CA, USA). Amplifications were carried out in the 384-well ABI veriti PCR System (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. PCR reactions (5 μL) consisted of 4 μL Master Mix and 1 μL DNA (20 ng/μL). Samples were heated at 94°C for 5 min, then subjected to 45 cycles of 94°C for 20 s, 56°C for 30 s, and 72°C for 1 m. Finally, reactions were incubated at 72°C for 3 min and held at 4°C.

Amplified fragments were genotyped using allele-specific mass spectrometry on a MassARRAY iPLEX MALDI-TOF platform (Sequenom) equipped with MassARRAY TYPER4.0 software. Procedures were supplied by BGI (Beijing, China).

2.4 | Statistical analysis

Statistical analysis was performed using SPSS 17.0 (IBM, Chicago, IL, USA). The distribution of SNP genotypes in controls was compared against the predictions of Hardy-Weinberg equilibrium (HWE) using the goodness-of-fit chi-squared test. Characteristics of NPC patients and controls were compared using the unpaired *t* test or chi-squared test, depending on the type of variable and normality of the data. Binary logistic regression was performed to estimate the association between SNP genotypes and NPC risk; odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated with and without adjustment for age, sex, and smoking history. All *P* values refer to two-sided tests, with $P<.05$ considered significant.

3 | RESULTS

3.1 | Characteristics of patients and controls

Genotype at the *APEX1* SNP rs1760944 was successfully determined in all 477 NPC patients and 558 cancer-free controls in our study. While the two groups did not differ significantly in age ($P=.076$), they did differ significantly in gender composition and smoking status ($P<.001$, Table 1). In addition, a significantly larger proportion of patients than controls was positive for Epstein-Barr virus (EBV)-related

TABLE 1 Clinical characteristics of nasopharyngeal carcinoma patients and cancer-free controls

Characteristics	NPC	Control	*P*
Age, y	46.68±11.60	48.06±13.48	.076
Sex			
Male	365	320	
Female	112	238	<.001
Smoking history			
Yes	163	118	
No	314	440	<.001
EBV-VCA-IgA			
Positive	314	14	
Negative	163	544	<.001

EBV-VCA-IgA, IgA against Epstein-Barr viral capsid antigen; NPC, nasopharyngeal carcinoma; y, year.
Values shown are n or mean±SD.

antibody (*P*<.001). Genotype frequencies at rs1760944 in the control group were consistent with HWE (*P*=.851; Table 2).

3.2 | Association of rs1760944 polymorphism with risk of NPC: all participants

The genotypes GT or GG at rs1760944 were significantly less frequent among patients than controls (60.38% vs 67.92%), and unconditional logistic regression indicated lower NPC risk in individuals with either of these genotypes than in individuals with the genotype TT (OR 0.720, 95%CI 0.557-0.929, *P*=.012). Controlling for age, sex, and smoking history caused OR to increase to 0.745 (95%CI 0.573-0.970, *P*=.029).

3.3 | Association of rs1760944 polymorphism with risk of NPC: subgroup analysis

Among patients older than 40 years, genotypes GT or GG were associated with significantly lower NPC risk than TT (OR 0.711, 95%CI 0.523-0.966, *P*=.029; Table 3). Adjusting for sex and smoking history led to an OR of 0.756 (95%CI 0.551-1.038, *P*=.084).

Among women, genotypes GT or GG were associated with significantly lower NPC risk than TT (OR 0.586, 95%CI 0.366-0.936, *P*=.025). Controlling for age and smoking history led to an OR of 0.634 (95%CI 0.373-1.078, *P*=.092).

Among individuals with no smoking history, genotypes GT or GG were associated with significantly lower NPC risk than TT (OR 0.653, 95%CI 0.482-0.885, *P*=.006). Adjusting for sex and age led to an OR of 0.679 (95%CI 0.494-0.934, *P*=.017).

4 | DISCUSSION

In this study involving subjects from an endemic region, we found that the genotypes GT or GG at APEX1 rs1760944 were significantly less frequent in NPC patients than in controls, even after adjusting for sex, age and smoking history. This result suggests that this SNP may be associated with susceptibility to NPC, and specifically that genotypes GT or GG may confer reduced risk for disease in the populations from endemic areas. This is consistent with another study in a Chinese population from a different part of the country, which found a tendency for genotype GG to be associated with lower NPC risk.[7]

How this SNP may affect APEX1 expression or activity is unclear. Since rs1760944 lies in the *APEX1* promoter region, genotype GG may influence promoter activity and increase the level of APEX1 protein expression.[19] We suggest that the genotypes GG and GT in rs1760944 may lead to higher expression of APEX1 than genotype TT, and therefore, greater capacity to repair oxidative damage. This would explain why GG and GT appeared to protect against NPC in our study.

This protective effect may be age-dependent: genotypes GT or GG conferred a protective effect that was marginally significant (*P*=.084) among individuals older than 40 years. Oxidative damage is usually much greater in older individuals,[20] and this may be one of the main drivers of NPC onset in those above 40. APEX1 upregulation in the presence of genotypes GT or GG may increase repair capacity, helping to decrease this oxidative damage and reduce NPC risk.

Similar reasoning may explain why we observed a marginally significant protective effect of genotypes GT or GG among women in our study (*P*=.092). Women aged 40-60 years accounted for over half of NPC female patients (64/112) and female controls (141/238). In addition to greater oxidative damage due simply to age, women in this age group are at higher risk of mood disorders, such as emotional depression due to menopausal symptoms and fluctuation of postmenopausal estradiol and follicle-stimulating hormone.[21] It is possible that these mood disorders are associated with higher levels of reactive oxidant species and oxidative stress, leading in turn to greater risk of many diseases, including cancer. APEX1 upregulation in the presence of genotypes GT or GG may increase repair capacity and thereby reduce NPC risk.

Our results suggest that the protective effect conferred by genotypes GT or GG depends on smoking status: the reduced risk was observed among never-smokers, but not among ever-smokers. The converse was observed in a previous study of a Chinese population from a different part of the country.[7] This discrepancy may reflect our small sample of ever-smokers, highlighting the need for larger studies in the future. The discrepancy may also reflect differences between the two study populations: ours was from the NPC endemic Guangxi region, while those in the previous study came from the non-endemic Chongqing region. Previous work has already shown that APEX1 SNPs may be associated with different effects depending on the environment[16] and cell type.[14,22] Whatever be the cause(s) of the discrepancy between our two studies, the larger question of whether and how smoking contributes to NPC risk is unclear. While cigarette smoking can generate free radicals that increase oxidative and nitrative stress and thereby increase risk of NPC,[23,24] some studies have found levels of the oxidative stress marker, 8-hydroxydeoxyguanosine (8-OHdG) in smokers were not significantly higher[25,26] or were lower

TABLE 2 Genotype frequencies at *APEX1* rs1760944 in nasopharyngeal carcinoma patients and cancer-free controls

	N (%)						
Genotype	**NPC**	**Control**	**OR (95%CI)**	***P***	**Adjusted OR[a] (95%CI)**	P_{adjust}	P_{HWE}
GT+GG	288 (60.38)	379 (67.92)	0.720 (0.557-0.929)	.012	0.745 (0.573-0.970)	.029	.851
TT	189 (39.62)	179 (32.08)					

APEX1, apurinic/apyrimidinic endodeoxyribonuclease 1; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; NPC, nasopharyngeal carcinoma; OR, odds ratio.

[a]Calculated by multiple logistic regression after adjusting for age, sex, and smoking history.

TABLE 3 Distribution of *APEX1* rs1760944 genotypes in nasopharyngeal carcinoma patients after stratification by age, sex, or smoking history

Subgroup	n (case/control)	No. of patients/controls with genotype		OR (95%CI)	*P*	Adjusted OR[a] (95%CI)	P_{adjust}
		GT+GG	TT				
Age, y							
≤40	139/154	76/95	63/59	0.724 (0.453-1.156)	NS	0.719 (0.447-1.158)	NS
>40	338/404	212/284	126/120	0.711 (0.523-0.966)	.029	0.756 (0.551-1.038)	.084
Sex							
Male	365/320	222/210	143/110	0.813 (0.595-1.111)	NS	0.807 (0.589-1.105)	NS
Female	112/238	66/169	46/69	0.586 (0.366-0.936)	.025	0.634 (0.373-1.078)	.092
Smoking history							
Yes	163/118	100/73	63/45	0.978 (0.601-1.593)	NS	1.014 (0.608-1.689)	NS
No	314/440	188/306	126/134	0.653 (0.482-0.885)	.006	0.679 (0.494-0.934)	.017

APEX1, apurinic/apyrimidinic endodeoxyribonuclease 1; CI, confidence interval; NS, not significant; OR, odds ratio; y, year.
[a]Calculated by multiple logistic regression after controlling for the other two stratifying factors. For instance, the adjusted OR for different gender subgroups was adjusted for age and smoking history.

than the levels in non-smokers.[27] Our own preliminary studies have also found a tendency toward higher serum levels of 8-OHdG among never-smokers with NPC than among ever-smokers with NPC (data not shown). We interpret these findings to indicate that cigarette smoking is likely to be only one of several factors that induce oxidative stress. Other factors include, for example, age and gender.[26,28.]

Whether the association between SNP rs1760944 and NPC risk depends on EBV infection cannot be addressed from our data. On one hand, the proportion of individuals positive for EBV-related antibody was significantly higher among NPC patients than among controls, suggesting that EBV-VCA-IgA status could be contributing to our results. On the other hand, frequencies of the genotypes GT or GG did not significantly differ between patients and controls for the subgroup of individuals positive for EBV-VCA-IgA or for the subgroup negative for EBV-VCA-IgA (data not shown). Larger studies are needed to address whether EBV infection affects the relationships between these SNPs and NPC risk, especially given the high proportion of controls (544/558) and low proportion of patients (163/477) who were negative for EBV-related antibody.

Although gender composition and smoking history differed significantly between patients and controls in our study (Table 1), we found no significant differences in genotype frequencies at rs1760944 between men and women or between never-smokers and ever-smokers (data not shown). Thus, it seems unlikely that this SNP varies with gender or smoking habit. In any event, we controlled for age, sex, and smoking status before performing stratification and adjustment analyses using logistic regression,[29] thereby minimizing any possible confounding of our results by these three factors.

Our results should be interpreted with caution because of several limitations. First, our relatively small sample may mean higher risk of selection bias. Second, because of our cross-sectional design, we cannot exclude that some controls will go on to have malignant tumors including NPC. Third, we examined only one SNP in the *APEX1* gene, leaving open the possibility that other polymorphisms influence risk of NPC. Similarly, we cannot exclude that other genes in the base excision repair pathway, such as *hOGG1* and *XRCC1*, also influence NPC risk.[30,31.]

5 | CONCLUSION

Our study suggests that the *APEX1* SNP rs1760944 may be associated with NPC risk in a population from an endemic area in South China, especially among those with no smoking history. Larger cohort studies are needed to clarify this association, especially among women and older individuals.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (81360406 and 81460415), the Guangxi Natural Science Foundation of China (2016GXNSFAA380096) and the Ministry of Education Key Laboratory for High-Incidence Tumor Prevention and Treatment foundation (GKE2015-ZZ10).

ETHICAL APPROVAL

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Ethics Committee of Guangxi Medical University, relevant Chinese law, and the 1964 Helsinki Declaration.

INFORMED CONSENT

Informed consent was obtained from all study participants.

REFERENCES

1. Wei Z, Zeng X, Xu J, Duan X, Xie Y. Prognostic value of pretreatment serum levels of lactate dehydrogenase in nonmetastatic nasopharyngeal carcinoma: single-site analysis of 601 patients in a highly endemic area. *Onco Targets Ther*. 2014;7:739-749.
2. Kong QL, Hu LJ, Cao JY, et al. Epstein-Barr virus-encoded LMP2A induces an epithelial-mesenchymal transition and increases the number of side population stem-like cancer cells in nasopharyngeal carcinoma. *PLoS Pathog*. 2010;6:e1000940.
3. Xu T, Su B, Wang C, et al. Molecular markers to assess short-term disease local recurrence in nasopharyngeal carcinoma. *Oncol Rep*. 2015;33:1418-1426.
4. Wang Z, Zeng Q, Chen T, et al. Silencing NFBD1/MDC1 enhances the radiosensitivity of human nasopharyngeal cancer CNE1 cells and results in tumor growth inhibition. *Cell Death Dis*. 2015;6:e1849.
5. Poon RY. DNA damage checkpoints in nasopharyngeal carcinoma. *Oral Oncol*. 2014;50:339-344.
6. Ma N, Kawanishi M, Hiraku Y, et al. Reactive nitrogen species-dependent DNA damage in EBV-associated nasopharyngeal carcinoma: the relation to STAT3 activation and EGFR expression. *Int J Cancer*. 2008;122:2517-2525.
7. Li Q, Wang JM, Peng Y, et al. Association of DNA base-excision repair XRCC1, OGG1 and APE1 gene polymorphisms with nasopharyngeal carcinoma susceptibility in a Chinese population. *Asian Pac J Cancer Prev*. 2013;14:5145-5151.
8. Wojcik KA, Synowiec E, Kaminska A, et al. Polymorphism of the APEX nuclease 1 gene in keratoconus and Fuchs endothelial corneal dystrophy. *Cell Mol Biol Lett*. 2015;20:48-65.
9. Dai ZJ, Shao YP, Kang HF, et al. Relationship between apurinic endonuclease 1 Asp148Glu polymorphism and gastrointestinal cancer risk: an updated meta-analysis. *World J Gastroenterol*. 2015;21:5081-5089.
10. Dai ZJ, Wang XJ, Kang AJ, et al. Association between APE1 single nucleotide polymorphism (rs1760944) and cancer risk: a meta-analysis based on 6,419 cancer cases and 6,781 case-free controls. *J Cancer*. 2014;5:253-259.
11. Kim YJ, Wilson DM 3rd. Overview of base excision repair biochemistry. *Curr Mol Pharmacol*. 2012;5:3-13.
12. Abbotts R, Madhusudan S. Human AP endonuclease 1 (APE1): from mechanistic insights to druggable target in cancer. *Cancer Treat Rev*. 2010;36:425-435.
13. Gu D, Wang M, Wang M, Zhang Z, Chen J. The DNA repair gene APE1 T1349G polymorphism and cancer risk: a meta-analysis of 27 case-control studies. *Mutagenesis*. 2009;24:507-512.
14. Lo YL, Jou YS, Hsiao CF, et al. A polymorphism in the APE1 gene promoter is associated with lung cancer risk. *Cancer Epidemiol Biomark Prev*. 2009;18:223-229.
15. Tong Z, Shen H, Yang D, et al. Genetic variations in the promoter of the APE1 gene are associated with DMF-induced abnormal liver function: a case-control study in a Chinese population. *Int J Environ Res Public Health*. 2016;13:752.
16. Zhou B, Shan H, Su Y, et al. The association of APE1 -656T > G and 1349 T > G polymorphisms and cancer risk: a meta-analysis based on 37 case-control studies. *BMC Cancer*. 2011;11:521.
17. Zhou K, Hu D, Lu J, et al. A genetic variant in the APE1/Ref-1 gene promoter -141T/G may modulate risk of glioblastoma in a Chinese Han population. *BMC Cancer*. 2011;11:104.
18. Kang H, Dai Z, Ma X, et al. A genetic variant in the promoter of APE1 gene (-656 T>G) is associated with breast cancer risk and progression in a Chinese population. *Gene*. 2013;531:97-100.
19. Hadi MZ, Coleman MA, Fidelis K, Mohrenweiser HW, Wilson DM 3rd. Functional characterization of Ape1 variants identified in the human population. *Nucleic Acids Res*. 2000;28:3871-3879.
20. Mariani E, Polidori MC, Cherubini A, Mecocci P. Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2005;827:65-75.
21. Hirose A, Terauchi M, Akiyoshi M, Owa Y, Kato K, Kubota T. Depressive symptoms are associated with oxidative stress in middle-aged women: a cross-sectional study. *Biopsychosoc Med*. 2016;10:12.
22. Jing B, Wang J, Chang WL, Li B, Chen J, Niu YJ. Association of the polymorphism of APE1 gene with the risk of prostate cancer in Chinese Han population. *Clin Lab*. 2013;59:163-168.
23. Xie Y, Wu Y, Zhou X, Yao M, Ning S, Wei Z. Association of polymorphisms hOGGI rs1052133 and hMUTYH rs3219472 with risk of nasopharyngeal carcinoma in a Chinese population. *Onco Targets Ther*. 2016;9:755-760.
24. Huang YJ, Zhang BB, Ma N, Murata M, Tang AZ, Huang GW. Nitrative and oxidative DNA damage as potential survival biomarkers for nasopharyngeal carcinoma. *Med Oncol*. 2011;28:377-384.
25. Besaratinia A, Van Schooten FJ, Schilderman PA, et al. A multi-biomarker approach to study the effects of smoking on oxidative DNA damage and repair and antioxidative defense mechanisms. *Carcinogenesis*. 2001;22:395-401.
26. Sakano N, Takahashi N, Wang DH, et al. Plasma 3-nitrotyrosine, urinary 8-isoprostane and 8-OHdG among healthy Japanese people. *Free Radical Res*. 2009;43:183-192.
27. Lettieri Barbato D, Tomei G, Tomei F, Sancini A. Traffic air pollution and oxidatively generated DNA damage: can urinary 8-oxo-7,8-di hydro-2-deoxiguanosine be considered a good biomarker? A meta-analysis *Biomarkers*. 2010;15:538-545.
28. Kanaya S, Ikeya M, Yamamoto K, et al. Comparison of an oxidative stress biomarker "urinary8-hydroxy-2'-deoxyguanosine", between smokers and non-smokers. *BioFactors*. 2004;22:255-258.
29. Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. *Gastroenterol Hepatol Bed Bench*. 2012;5:79-83.
30. Zhao Q, Wang W, Zhang Z, et al. A genetic variation in APE1 is associated with gastric cancer survival in a Chinese population. *Cancer Sci*. 2011;102:1293-1297.
31. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell*. 1996;86:353-364.

How to cite this article: Lu Z, Li S, Ning S, et al. Association of the rs1760944 polymorphism in the *APEX1* base excision repair gene with risk of nasopharyngeal carcinoma in a population from an endemic area in South China. *J Clin Lab Anal*. 2018;32:e22238. https://doi.org/10.1002/jcla.22238