Replication Study of ESCC Susceptibility Genetic Polymorphisms Locating in the ADH1B-ADH1C-ADH7 Cluster Identified by GWAS

Jiwen Wang1,2,*, Jinyu Wei3, Xiaoling Xu1, Wenting Pan3, Yunxia Ge3, Changchun Zhou4, Chao Liu5, Jia Gao6, Ming Yang3,*, Weimin Mao1,2,7

1 Cancer Research Institute, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China, 2 Key Laboratory of Diagnosis and Treatment Technology on Thoracic Oncology, Zhejiang Province, China, 3 College of Life Science and Technology, Beijing University of Chemical Technology, Beijing, China, 4 Clinical Laboratory, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, Shandong Province, China, 5 Clinical Laboratory, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China, 6 Clinical Laboratory, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, 7 Thoracic Surgery Department, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China

Abstract

China was one of the countries with highest esophageal squamous cell carcinoma (ESCC) incidence and mortality worldwide. Alcohol drinking has been identified as a major environmental risk-factor related to ESCC. The alcohol dehydrogenase (ADH) family are major enzymes involved in the alcohol-metabolizing pathways, including alcohol dehydrogenase 1B (ADH1B) and ADH1C. Interestingly, ADH1B and ADH1C genes locate tandemly with ADH7 in a genomic segment as a gene cluster, and are all polymorphic. Several ESCC susceptibility single nucleotide polymorphisms (SNPs) of the ADH1B-ADH1C-ADH7 cluster have been identified previously through a genome-wide association study (GWAS). In the study, we examined the association between five ADH1B-ADH1C-ADH7 cluster SNPs (rs1042026, rs17033, rs1614972, rs1789903 and rs17028973) and risk of developing ESCC. Genotypes were determined in two independent case-control sets from two regions of China. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression. Our data demonstrated that these ADH1B-ADH1C-ADH7 cluster SNPs confer susceptibility to ESCC in these two case-control sets, which were consistent to results of the previous GWAS.

Introduction

China was one of the countries with highest incidence and mortality of esophageal squamous cell carcinoma (ESCC) worldwide [1]. Epidemiological studies show that consumption of tobacco and alcohol are major risk factors for ESCC [2,3]. However, only a portion of individuals exposed to tobacco and alcohol develop ESCC, indicating the crucial role of host susceptibility factors in ESCC. Accumulated evidences suggested that single nucleotide polymorphisms (SNP) might explain individual differences of susceptibility to ESCC through the candidate gene approach or the genome-wide association study (GWAS) approach [4–17].

Alcohol drinking has been identified as a major environmental risk-factor related to ESCC [2,3]. Ethanol is metabolized in vivo by alcohol dehydrogenase (ADH) family and aldehyde dehydrogenase (ALDH), which are all polymorphic in human beings [18–19]. The total activity of ADH is significantly higher in cancer tissue than in healthy mucosa [18]. The ADH family and ADH polymorphisms influence individual diversity in alcohol-oxidizing capability and drinking behavior [19]. Among the ADH family, the major enzymes involved in the alcohol-metabolizing pathways are alcohol dehydrogenase 1B (ADH1B) and ADH1C. ADH1B and ADH1C exist as several homo- and heterodimers of ADH1A subunits, exhibit high activity for ethanol oxidation and play an essential role in ethanol catabolism. ADH7 is also a member of the ADH family. Although less efficient in ethanol oxidation compared to ADH1B or ADH1C, ADH7 is the most active as a retinol dehydrogenase. Therefore, ADH7 may take part in the synthesis of retinoic acid, a hormone important for cellular differentiation. Interestingly, the aforementioned three genes locate tandemly in a genomic segment as a gene cluster. Wu et al. identified several new ESCC susceptible SNPs, including ADH1B rs1042026 and rs17033, ADH1C rs1614972 and rs1789903 as well as ADH7 rs17028973 through a GWAS based on analyses of in 2003 ESCC cases and 2044 controls with independent validation in 8092 ESCC cases and 8620 controls [4]. Considering the importance of ADH1B-ADH1C-ADH7 cluster in ESCC, we conducted this replication case-control study to validate the association between ADH1B rs1042026 and rs17033, ADH1C rs1614972 and rs1789903, and ADH7 rs17028973 through a GWAS.


rs1614972 and rs1789903 as well as ADH7 rs17028973 SNPs and ESCC risk.

Materials and Methods

Study subjects

This study consisted of two case-control sets: (a) Hangzhou set: 617 patients with ESCC from Cancer Research Institute, Zhejiang Cancer Hospital (Hangzhou, Zhejiang Province, China) and sex-and age-matched (±5 years) 537 controls. Patients were recruited between January 2012 and March 2013 at Zhejiang Cancer Hospital. Control subjects were individuals who underwent a physical examination in the same hospital during the same time period as the patients were collected. (b) Jinan study: 540 patients with ESCC from Shandong Cancer Hospital, Shandong Academy of Medical Sciences (Jinan, Shandong Province, China) and sex-and age-matched (±5 years) 550 controls. Patients were recruited between June 2009 and April 2012 at Shandong Cancer Hospital. Control subjects were randomly selected from a pool of 4500 individuals from a community cancer-screening program for early detection of cancer conducted in Jinan city during the same time period as the patients were collected. The diagnosis of all patients was histologically confirmed. Individuals who smoked one cigarette per day for over 1 year were considered as smokers. Subjects were considered as alcohol drinkers, if they drank at least once per week. All subjects were ethnic Han Chinese.

Statistical analyses

Pearson’s $\chi^2$ test was used to examine the differences in demographic variables and genotype distributions of five $ADH1B$-$ADH1C$-$ADH7$ cluster SNPs between patients and controls. The associations between genotypes of these SNPs and ESCC risk were estimated by ORs and their 95% CIs computed by logistic regression models. All ORs were adjusted for age, sex, smoking or drinking status, where it was appropriate. We tested the null hypotheses of multiplicative gene-environment interaction and evaluated departures from multiplicative interaction models by including main effect variables and their product terms in the logistic regression model [4,20–23]. A $P$ value of less than 0.05 was used as the criterion of statistical significance, and all statistical tests were two-sided. All analyses were performed using Statistical Analysis System (version 9.0; SAS Institute) and SPSS 16.0 (SPSS Inc.).

Results

In terms of median age and sex distribution, no statistically significant differences were found between ESCC patients and healthy controls for Hangzhou set and Jinan set (all $P>0.05$), indicating that the frequency matching was appropriate (Table 1). However, there are more smokers and alcohol drinkers were observed among ESCC cases compared with controls in Jinan.
Table 2. Associations between candidate SNPs in the ADH1B-ADH1C-ADH7 cluster and ESCC risk in Hangzhou case-control set (Discovery set).

| Gene locus | Case | Position*1 | Position*2 | Position*3 | Position*4 | Position*5 |
|------------|------|------------|------------|------------|------------|------------|
| rs1042026  | ADH1B | 100447499  | Control    | 100447066  | Control    | 100441804  |
| rs17033    | ADH1B | 100447968  | Control    | 100447178  | Control    | 100441778  |
| rs1614972  | ADH1C | 100477178  | Control    | 100481064  | Control    | 100441809  |
| rs1789903  | ADH7  | 100541809  | Control    | 100541809  | Control    | 100541809  |

Note: SNP, single nucleotide polymorphism; CC, control group; T/C, wild type or mutant type; ADH1B, alcohol dehydrogenase 1B; ADH1C, alcohol dehydrogenase 1C; ADH7, alcohol dehydrogenase 7; OR, odds ratio; CI, confidence interval.

---

Firstly, unconditional logistic regression analysis was utilized to detect associations between five ADH1B-ADH1C-ADH7 cluster SNPs (rs1042026, rs17033, rs1614972, rs1789903 and rs17028973) and ESCC risk in Hangzhou discovery set (Table 2). All observed genotype frequencies in controls conform to Hardy–Weinberg equilibrium in Hangzhou set. Logistic regression analyses revealed that all five SNPs were significantly associated with ESCC risk (ADH1B rs1042026: allelic OR = 2.02, 95% CI = 1.66–2.47, P<0.001; ADH1B rs17033: allelic OR = 1.58, 95% CI = 1.18–2.11, P=0.001; ADH1C rs1614972: allelic OR = 1.65, 95% CI = 1.36–2.00, P<0.001; ADH1C rs1789903: allelic OR = 1.77, 95% CI = 1.33–2.35, P<0.001; ADH7 rs17028973: allelic OR = 1.61, 95% CI = 1.35–1.92, P<0.001) (Table 2). The ADH1B rs1042026 A allele, ADH1B rs17033 G allele, ADH1C rs1614972 C allele, ADH1C rs1789903 G allele, and ADH7 rs17028973 T allele were showed to be risk alleles.

Associations between genotypes of five ADH1B-ADH1C-ADH7 cluster SNPs and risk of ESCC were estimated in Hangzhou discovery set (Table 3). Individuals with the ADH1B rs1042026 AG or AA genotype had an OR of 1.54 (95% CI = 1.19–1.98, P=0.001) or 5.40 (95% CI = 3.19–9.11, P<0.001) for developing ESCC, respectively, compared with individuals with the GG genotype (Table 3). ADH1B rs17033 AG carriers showed a 1.67-fold increased ESCC risk compared with those carrying the GG genotype (95% CI = 1.24–2.26, P=0.001) (Table 3). A significantly increased ESCC risk associated with the ADH1C rs1614972 TC or CC genotype compared with the TT genotype was observed (OR = 1.70; 95% CI = 1.26–2.30 or OR = 5.50; 95% CI = 2.19–13.02, P=0.001) (Table 3). The presence of the ADH7 rs1614972 CC genotype was also associated with increased risk of ESCC (OR = 3.07, 95% CI = 1.21–25.0, respectively) compared with the absence of such a genotype. Moreover, the ADH7 rs17028973 TT genotype were significantly associated with increased risk of ESCC (OR = 3.49, 95% CI = 0.94–13.02, P=0.062). Additionally, ADH7 rs17028973 TT carriers showed a 2.62-fold increased ESCC risk compared with those carrying the CC genotype in the validation set (95% CI = 1.75–3.93, P<0.001) (Table 3).

The ESCC risk associated with the ADH1B-ADH1C-ADH7 cluster SNPs was further examined by stratifying for smoking and drinking status of controls in Hangzhou case-control set.
Table 3. Genotype frequencies of the ADH1B-ADH1C-ADH7 cluster SNPs among cases and controls and their association with ESCC risk.

| Genotypes | Hangzhou case-control set | Jinan case-control set |
|-----------|---------------------------|------------------------|
|           | Cases, No. (%) | Controls, No. (%) | OR^1 (95% CI) | p^3 | Cases, No. (%) | Controls, No. (%) | OR^1 (95% CI) | p^3 |
| ADH1B rs1042026 | n = 615 | n = 537 | | | n = 540 | n = 550 | | |
| GG | 314(51.1) | 358(66.7) | 1.00 (Reference) | | 285(52.8) | 366(66.5) | 1.00 (Reference) | |
| AG | 216(35.1) | 160(29.8) | 1.54(1.19–1.98) | 0.001 | 184(34.1) | 165(30.0) | 1.47(1.12–1.91) | 0.005 |
| AA | 85(13.8) | 19(3.5) | 5.40(3.19–9.11) | <0.001 | 71(13.1) | 19(3.5) | 4.53(2.65–7.72) | <0.001 |
| ADH1B rs17033 | n = 617 | n = 536 | | | n = 540 | n = 550 | | |
| AA | 471(76.3) | 452(84.3) | 1.00 (Reference) | | 417(77.2) | 464(84.4) | 1.00 (Reference) | |
| AG | 146(23.7) | 84(15.7) | 1.67(1.24–2.26) | 0.001 | 123(22.8) | 86(15.6) | 1.58(1.16–2.16) | 0.004 |
| ADH1C rs1614972 | n = 617 | n = 537 | | | n = 540 | n = 550 | | |
| TT | 302(49.3) | 324(60.3) | 1.00 (Reference) | | 271(50.2) | 332(60.4) | 1.00 (Reference) | |
| TC | 239(39.0) | 190(35.4) | 1.35(1.06–1.73) | 0.016 | 207(38.3) | 195(35.4) | 1.30(1.01–1.68) | 0.045 |
| CC | 76(11.7) | 23(4.3) | 3.59(2.19–5.88) | <0.001 | 62(11.5) | 23(4.2) | 3.15(1.88–5.26) | <0.001 |
| ADH1C rs1789903 | n = 617 | n = 536 | | | n = 540 | n = 550 | | |
| CC | 465(75.4) | 453(84.5) | 1.00 (Reference) | | 413(76.5) | 464(84.4) | 1.00 (Reference) | |
| CG | 141(22.9) | 81(15.1) | 1.70(1.26–2.30) | 0.001 | 117(21.7) | 83(15.1) | 1.58(1.15–2.16) | 0.005 |
| GG | 11(1.8) | 2(0.4) | 5.50(3.21–25.0) | 0.027 | 10(1.9) | 3(0.5) | 3.49(0.94–13.02) | 0.062 |
| ADH7 rs17028973 | n = 617 | n = 536 | | | n = 540 | n = 550 | | |
| CC | 237(38.4) | 262(48.9) | 1.00 (Reference) | | 212(39.3) | 270(49.1) | 1.00 (Reference) | |
| CT | 262(42.5) | 231(43.1) | 1.25(0.98–1.61) | 0.078 | 232(43.0) | 236(42.9) | 1.26(0.97–1.63) | 0.082 |
| TT | 118(19.1) | 43(8.0) | 3.07(2.07–4.54) | <0.001 | 96(17.8) | 44(8.0) | 2.62(1.75–3.93) | <0.001 |

Note: SNP, single nucleotide polymorphism; ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

^1Data were calculated by logistic regression with adjustment for age, sex, smoking and drinking status, where it was appropriate.

doi:10.1371/journal.pone.0094096.t003
### Table 4. Risk of ESCC associated with the ADH1B rs1042026 and rs17033 SNPs by smoking status and drinking history in Jinan set.

| Variable | ADH1B rs1042026 | | | | ADH1B rs17033 | | | |
|----------|-----------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|          | GG1 | AG+AA1 | OR2 (95% CI) | P | AA1 | GG1 | OR2 (95% CI) | P |          |          |          |          |          |          |          |
| Smoking status |                |                |                |    |                |                |                |    |                |                |                |                |                |                |                |
| No       | 104/177 | 82/88  | 1.58 (1.06–2.35) | 0.026 | 149/229 | 37/36 | 1.58 (0.93–2.66) | 0.089 |            |            |            |            |            |            |
| Yes      | 181/189 | 173/96 | 1.96 (1.40–2.77) | <0.001 | 268/235 | 86/50 | 1.65 (1.09–2.49) | 0.017 |            |            |            |            |            |            |
| Alcohol drinking |                |                |                |    |                |                |                |    |                |                |                |                |                |                |                |
| No       | 126/193 | 114/106 | 1.61 (1.13–2.30) | 0.008 | 180/254 | 60/45 | 1.71 (1.10–2.66) | 0.017 |            |            |            |            |            |            |
| Yes      | 159/173 | 141/78  | 1.97 (1.37–2.82) | <0.001 | 237/210 | 63/41 | 1.41 (0.90–2.20) | 0.134 |            |            |            |            |            |            |

Note: SNP, single nucleotide polymorphism; ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

1. Number of patients with genotype/number of control subjects with genotype.
2. Data were calculated by logistic regression, adjusted for sex, age, smoking and drinking history, where it was appropriate.
3. P values for gene-environment interaction were calculated using the multiplicative interaction term in SPSS software.

doi:10.1371/journal.pone.0094096.t004

### Table 5. Risk of ESCC associated with the ADH1C rs1614972 and rs1789903 and ADH7 rs17028973 SNPs by smoking status and drinking history in Jinan set.

| Variable | ADH1C rs1614972 | | | | ADH1C rs1789903 | | | | | ADH7 rs17028973 | | |
|----------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|          | TTa | TC+CC1 | OR2 (95% CI) | P | CC1 | CG+GG1 | OR2 (95% CI) | P | CC1 | CT+TT1 | OR2 (95% CI) | P |          |          |          |          |          |          |          |          |
| Smoking status |                |                |                |    |                |                |                |    |                |                |                |                |                |                |                |                |                |                |                |
| No       | 98/160 | 88/105  | 1.42 (0.96–2.11) | 0.081 | 149/218 | 37/47 | 1.28 (0.78–2.11) | 0.336 | 85/131 | 127/139 | 1.12 (0.76–1.66) | 0.556 |            |            |            |            |            |            |
| Yes      | 173/172 | 181/133 | 1.65 (1.18–2.31) | 0.003 | 264/246 | 90/39 | 2.10 (1.36–3.25) | 0.001 | 127/139 | 227/146 | 1.83 (1.30–2.57) | 0.001 |            |            |            |            |            |            |
| Alcohol drinking |                |                |                |    |                |                |                |    |                |                |                |                |                |                |                |                |                |                |                |
| No       | 119/179 | 121/120 | 1.47 (1.04–2.08) | 0.031 | 183/248 | 57/51 | 1.50 (0.97–2.31) | 0.065 | 98/146 | 142/153 | 1.37 (0.97–1.94) | 0.076 |            |            |            |            |            |            |
| Yes      | 152/153 | 148/98  | 1.55 (1.09–2.20) | 0.014 | 230/216 | 70/35 | 1.85 (1.17–2.92) | 0.008 | 114/124 | 186/127 | 1.63 (1.15–2.32) | 0.006 |            |            |            |            |            |            |

Note: SNP, single nucleotide polymorphism; ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

1. Number of patients with genotype/number of control subjects with genotype.
2. Data were calculated by logistic regression, adjusted for sex, age, smoking and drinking history, where it was appropriate.
3. P values for gene-environment interaction were calculated using the multiplicative interaction term in SPSS software.

doi:10.1371/journal.pone.0094096.t005
status and alcohol drinking history due to the key role of these enzymes in metabolism of ethanol and other toxins in Jiamin case-control set (Table 4 and 5). Interestingly, we found higher odds of those five polymorphisms for developing ESCC among smokers than those among non-smokers (Table 4 and 5). Similar results were also observed among alcohol drinkers except ADH1B rs17033 genetic variant (Table 4 and 5). However, no evident gene-smoking interaction or gene-drinking interaction exists in Jiamin case-control set (Table 4 and 5). We also examined whether there are gene-environment interaction between five ADH1B-ADH1C-ADH7 cluster genetic variants and age and sex, but the results were negative (data not shown).

Discussion

In the current study, we examined the association between five ADH1B-ADH1C-ADH7 cluster SNPs (rs1042026, rs17033, rs1614972, rs1789903 and rs17028973) and risk of developing ESCC in a two-stage case-control design. In this replication study, we successfully validated results of a previous GWAS that these five SNPs confer susceptibility to ESCC [4]. However, no significant gene-smoking interaction or gene-drinking interaction between these ADH1B-ADH1C-ADH7 polymorphisms and ESCC was observed in this Chinese Han population.

Several molecular epidemiological studies using a candidate gene approach indicated a set of SNPs associated with ESCC susceptibility, primarily variations that are related to alcohol metabolism [24–30]. As a powerful and successful tool to identify common disease alleles, GWAS could interrogate a large amount of tagging SNPs that serve as surrogates for untested common SNPs across the genome. In published GWAS of cancers of the upper aerodigestive tract, including ESCC in individuals of European [28,30], Japanese [9] and Chinese [4], have shown that SNPs in the ADH genes contribute to susceptibility of ESCC. Our results in this study are consistent to these reports and highlight the importance of genetic variants of the ADH genes in ESCC development.

There might be several limitations in the current case-control study. First, because it was a hospital-based study and there were a few in the hospital, inherent selection bias may exist. Thus, it is important to validate these findings in a population-based prospective study from the same geographic regions. Second, the statistical power of our study may be limited by the sample size, especially for statistical analyses of gene-covariate interaction. Third, future studies will need to address the biological function of these polymorphisms in the genesis of ESCC.

In summary, our study elucidated that the ADH1B-ADH1C-ADH7 cluster polymorphisms were associated with risk of ESCC in Chinese populations. Our data support the hypothesis that multiple ADH genes are involved in ESCC etiology and highlight the importance of genetic components in cancer development [31–41].

Acknowledgments

We thank Xiaohui Tang, Meng Li, Juan Shi, Chao Lu, Xiaojiang Zhang, and Li Liu for their technical supports and all the subjects of this study for their participation.

Author Contributions

Conceived and designed the experiments: MY WM. Performed the experiments: J. Wang J. Wei. Analyzed the data: J. Wang J. Wei XX WP YG MY. Contributed reagents/materials/analysis tools: CZ CL JG. Wrote the paper: MY J. Wang.
27. Hashibe M, McKay JD, Curado MP, Oliveira JC, Koifman S, et al. (2008) Multiple ADH genes are associated with upper aerodigestive cancers. Nat Genet 40:707–709.
28. Akbari MR, Malekzadeh R, Shakeri R, Nasrollahzadeh D, Foumani M, et al. (2009) Candidate gene association study of esophageal squamous cell carcinoma in a high-risk region in Iran. Cancer Res 69:7994–8000.
29. Wu M, Chang SC, Kampman E, Yang J, Wang XS, et al. (2013) Single nucleotide polymorphisms of ADH1B, ADH1C and ALDH2 genes and esophageal cancer: a population-based case-control study in China. Int J Cancer 132:1868–1877.
30. McKay JD, Truong T, Gaborieau V, Chabrier A, Chaang SC, et al. (2011) A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. PLoS Genet 7:e1001333.
31. Zheng J, Deng J, Xiao M, Yang L, Zhang L, et al. (2013) A sequence polymorphism in miR-608 predicts recurrence after radiotherapy for nasopharyngeal carcinoma. Cancer Res 73:5151–5162.
32. Zheng J, Liu B, Zhang L, Jiang L, Huang B, et al. (2012) The protective role of polymorphisms M KK4+1304 T>G in nasopharyngeal carcinoma is modulated by Epstein-Barr virus' infection status. Int J Cancer 130:1981–1990.
33. Liu L, Wu C, Wang Y, Zhong R, Wang F, et al. (2011) Association of candidate genetic variations with gastric cardia adenocarcinoma in Chinese population: a multiple interaction analysis. Carcinogenesis 32:336–342.
34. Zhong R, Liu L, Zou L, Sheng W, Zhu B, et al. (2013) Genetic variations in the TGFβ signaling pathway, smoking and risk of colorectal cancer in a Chinese population. Carcinogenesis 34:936–942.
35. Chen W, Song H, Zhong R, Zhu B, Guo H, et al. (2013) Risk of GWAS-identified genetic variants for breast cancer in a Chinese population: a multiple interaction analysis. Breast Cancer Res Treat 142:637–644.
36. Zhong R, Liu L, Tian Y, Wang Y, Tian J, et al. (2014) Genetic variant in SWI/SNF complexes influences hepatocellular carcinoma risk: a new clue for the contribution of chromatin remodeling in carcinogenesis. Sci Rep 4:4147.
37. Yao J, Liu L, Yang M (2014) Interleukin-23 receptor genetic variants contribute to susceptibility of multiple cancers. Gene 533:21–25.
38. Li Z, Liu W, Li D, Liu L, Wei J, et al. (2014) Association of functional FEN1 genetic variants and haplotypes and breast cancer risk. Gene 538:42–45.
39. Liu J, Tang X, Li M, Lu C, Shi J, et al. (2013) Functional MDM4 rs4245739 genetic variant, alone and in combination with P53 Arg72Pro polymorphism, contributes to breast cancer susceptibility. Breast Cancer Res Treat 140:151–157.
40. Liu L, Wu G, Xue F, Li Y, Shi J, et al. (2013) Functional CYP1A1 genetic variants, alone and in combination with smoking, contribute to development of head and neck cancers. Eur J Cancer 49:2143–2151.
41. Chen YD, Zhang X, Qiu XG, Li J, Yuan Q, et al. (2013) Functional FEN1 genetic variants and haplotypes are associated with glioma risk. J Neurooncol 111:145–151.