

# ADH7 Polymorphism and Alcohol Consumption on Risk of Head and Neck Squamous Cell Carcinoma in The Korean Population

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## Research Article

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## Abstract

### Purpose

The development of head and neck squamous cell carcinoma (HNSCC) is closely associated with alcohol consumption. Also, it is related to individual genetic susceptibility, such as single nucleotide polymorphism (SNP) of alcohol dehydrogenase (ADH). This study aimed to investigate the association of *ADH7* SNPs with the risk of HNSCC.

### Methods and Patients:

We analyzed *ADH7* rs1573496C > G, rs3737482T > C, rs1154460G > A, and rs284787T > C SNPs in 250 patients with HNSCC and 322 controls in the Korean populations. Genomic DNA was extracted from peripheral blood, and genotyping was done using the TaqMan assay. Linkage disequilibrium (LD) and haplotypes were analyzed.

### Results

The odds ratios (OR) and 95% confidence intervals (CI) of the CT and CC genotypes of *ADH7* rs3737482T > C were 0.48 (0.29–0.78) and 0.69 (0.49–0.96), indicating a significantly decreased risk. In SNP of rs1154460G > A, the OR and 95% CI of the AA genotype was 1.63 (1.11–2.40), showing a significant increase in the risk. Furthermore, SNPs of *ADH7* rs3737482T > C and *ADH7* rs1154460G > A exhibit synergistic interactions with alcohol composition on the risk of HNSCC. None of the haplotypes were associated with the risk of HNSCC.

### Conclusions

*ADH7* rs3737482T > C and rs1154460G > A SNPs are associated with the risk of development of HNSCC in Koreans. It could serve as a molecular biological marker to screen the high-risk groups for HNSCC.

### Introduction

Alcohol consumption is closely associated with the development of head and neck squamous cell carcinoma (HNSCC) [1-3]. Many previous case-control studies and prospective researches reported that a certain amount of daily alcohol intake increases the risk of cancer in the oral cavity, pharynx, larynx, and esophagus [4,5]. The International Agency for Research on Cancer (IARC) concluded that alcohol was confirmed as a causative factor in the development of oral cavity, pharynx, larynx, esophagus, breast, liver, and colon cancer [4].

Ingested ethanol is oxidized to acetaldehyde mainly by alcohol dehydrogenase (ADH), and acetaldehyde is oxidized again to non-toxic acetate by aldehyde dehydrogenase (ALDH). Among these, acetaldehyde has been reported to play an important role in inducing tumors [6-8]. Also, the acetaldehyde concentration is found to be 10–20 times higher in saliva than in blood after drinking alcohol, which is considered to be associated with head and neck cancer [9].

Although alcohol consumption is the important risk factor for the development of HNSCC, host-related factors such as genetic polymorphism, which depends on the genetic differences of individuals, are also risk factors [10,11]. Altered genotypes of ADH, which may be responsible for the rapid metabolism of ethanol to acetaldehyde, exhibit a higher level of acetaldehyde in the body and, eventually, exhibit an increased risk of malignant tumors [12-15]. There are 7 isoenzymes in 5 classes partitioned according to nucleotide sequence similarity: *ADH1A*, *ADH1B*, *ADH1C* in class I, *ADH4* in class II, *ADH5* in class III, *ADH7* in class IV, and *ADH6* in class V [16].

Most of the studies on ADH polymorphism of head and neck cancer were about *ADH1B* and *ADH1C* polymorphism [12-15,17,18]. Studies about *ADH7* SNP are rare. Only a few studies exist on the association between *ADH7* SNPs and the risk of head and neck cancer [19-23]. Even at that, those studies showed conflicting results [19-23]. There has been no study on *ADH7* SNPs of head and neck cancer in South Korea. Therefore, in this study, we investigated the SNPs of *ADH7* and their relationship with the risk of head and neck squamous cell carcinoma (HNSCC) in Koreans.

### Materials And Methods

This study was approved by the Institutional Review Board (IRB) of Hanyang University (IRB number: HYG-12-001), and informed consent was obtained from all participants.

#### Subjects

Two hundred and eighty patients with HNSCC who were treated in the Department of Otolaryngology and Head and Neck Surgery at Hanyang University Hospital from January 2000 to December 2004 were enrolled in this study as the cases. The control group included 330 patients who were hospitalized during the same period for chronic sinusitis, chronic otitis media, and chronic tonsillitis. Those with a history of malignant tumors at other sites or specific genetic disorders were excluded. We calculated the sample size using a two-sided test with the predicted odds ratio of 0.78, a significance level of 0.05, and a power of 80%. All the participants of this study were of Korean nationality and were living in South Korea at the time the study was carried out.

The participants were divided according to their alcohol consumption history: non-drinkers and drinkers. Also, the drinker group was categorized into social drinkers who consumed alcohol at a rate of less than 120 g per week and heavy drinkers who consumed more than 120 g per week.

## Methods

### DNA extraction

A 10-ml sample of peripheral blood was collected in a tube containing EDTA, stored at  $-70^{\circ}\text{C}$ , and used for the experiment. DNA from the peripheral blood was extracted using Wizard<sup>TM</sup> Genomic DNA purification kit (Promega, Madison, WI, USA).

### Genetic analysis

*ADH7* rs1573496C>G, rs3737482T>C, rs1154460G>A, and rs284787 T>C were analyzed using the TaqMan assay method. The forward and reverse primers used in the experiments are showed in Table 1. Polymerase chain reaction (PCR) was performed using a 5- $\mu\text{l}$  sample of the mixture made of TaqMan universal PCR master mix (Applied Biosystems, Foster City, CA, USA), UNG, 900 $\mu\text{M}$  of each primer, 200 nM of each probe, and 20 $\mu\text{g}$  of genomic DNA. The experiment was carried out at  $50^{\circ}\text{C}$  for 2 minutes and at  $95^{\circ}\text{C}$  for 10 minutes for reaction, followed by denaturing at  $95^{\circ}\text{C}$  for 15 seconds, and annealing and extension at  $60^{\circ}\text{C}$  for 1 minute, which results in a 40-fold amplification. The 12 positive samples and 12 negative blank controls were used instead of quantitative RT-PCR. The TaqMan assay plate was moved to the Prism 9700HT instrument (Applied Biosystems), and the fluorescent intensity of each well was measured for the genetic analysis with SDS software ver. 2.3. (Applied Biosystems, Foster City, CA, USA).

### Haplotype analysis

Linkage disequilibrium (LD) was analyzed using Haploview v4.2 software. Lewontin's  $D'$  ( $|D'|$ ), and the LD coefficient  $r^2$  between all pairs of biallelic loci were examined. Haplotypes were estimated using PHASE v2.0 software from the University of Washington. In *ADH7* SNPs, three types of haplotype showing more than 5% of frequency observed in rs3737482T>C and rs1154460G>A were analyzed.

### Statistics

For the statistical analyses of differences in demographic variables and *ADH7* SNP between the HNSCC patients and the control group, the Student's  $t$ -test was used for continuous variables, while the chi-square test and Fisher's exact test were used for categorical variables. Odds ratio (OR) and 95% confidence interval (CI) for genetic polymorphisms were calculated using logistic regression analysis after adjusting for sex, age, and alcohol consumption. Univariate analyses were performed using the referent model (heterozygotes vs. major homozygotes and minor homozygotes vs. major homozygotes) and three alternative models: 1) the co-dominant model (minor allele homozygotes vs. heterozygotes vs. major allele homozygotes); 2) the dominant model for minor alleles (minor allele homozygotes plus heterozygotes vs. major allele homozygotes); and 3) the recessive model for minor alleles (minor allele homozygotes vs. heterozygotes plus major allele homozygotes). SPSS (version 18.0, SPSS Inc, Chicago, Illinois, USA) was used for statistical analysis. A  $p$ -value less than 0.05 was considered statistically significant.

## Results

Of the 280 cases and 330 controls enrolled in the case and control groups, *ADH7* genotyping was performed successfully in 250 of 280 participants in the case group and in 322 of 330 participants in the control group. We conducted a case-control study involving those participants with successful genotyping.

### Characteristics of the participants

The average age of the case group was 62.2 (28–86 years) and 43.8 (21–76 years) in the control group, showing a higher average age in the case group than in the control group ( $P<0.001$ ). There were 219 males and 31 females in the case group and 305 males and 17 females in the control group. Significantly more heavy drinkers were found in the case group compared to the control group ( $P<0.001$ ). By primary sites of HNSCC, there were 120 patients with laryngeal cancer, 64 patients with oral cavity cancer, 31 patients with oropharyngeal cancer and, 35 patients with hypopharyngeal cancer.

### *ADH7* allele frequency

The allele frequencies of *ADH7* rs1573496C>G, rs3737482T>C, rs1154460G>A, and rs284787T>C were examined (Table 2). All genetic polymorphisms fit the Hardy-Weinberg equilibrium.

### *ADH7* polymorphism and risk of head and neck squamous cell carcinoma

In *ADH7* rs1573496C>G, the frequencies were 100% only in the CC genotype in the case group, and the frequencies of CC, CG, and GG genotypes were 99.7%, 0.3%, and 0%, respectively, in the control group. The odds ratio was undetermined (Table 3).

In *ADH7* rs3737482T>C, the frequencies of the three genotypes TT, CT, and CC were 37.2%, 44.4%, 18.4%, respectively, in the case group and 25.2%, 52.5%, 22.4% in the control group, respectively (Table 3). Based on the TT genotype, the OR of the CT genotype was 0.48(95% CI: 0.29–0.78), and the OR of the CC genotype was 0.69(95% CI: 0.49–0.96), showing significantly low odds ratios in both genotypes.

In *ADH7* rs1154460G>A, the frequencies of the three genotypes GG, AG, and AA were 37.6%, 48.0%, 14.4%, respectively, in the case group and 42.2%, 48.8%, 9.0%, respectively, in the control group (Table 3). Based on the GG genotype, the OR of the AG genotype was 1.47(95% CI: 1.06–2.04) and 2.03(95% CI: 1.05–

3.92), in the co-dominant and recessive models, respectively, while the OR of the AA genotype was 1.63(95% CI: 1.11–2.40) in the referent model, showing a significantly higher odds ratio in the AA genotype.

In *ADH7* rs284787T>C, the frequencies of the three genotypes TT, CT, and CC were 40.4%, 47.2%, 12.4%, respectively, in the case group and 45.7%, 42.2%, 12.1%, respectively, in the control group (Table 3). Based on the TT genotype, the OR of the CT genotype was 1.43(95% CI: 0.90–2.28), and the CC genotype was 1.24(95% CI: 0.87–1.74). Neither genotype showed statistically significant differences.

### Linkage disequilibrium and haplotype of *ADH7*

In the analysis of *ADH7* linkage disequilibrium, high linkage disequilibrium occurred only between rs3737482T>C and rs1154460G>A (Figure 1). Three types of haplotype were found showing more than 5% of frequency observed in *ADH7* rs3737482T>C and rs1154460G>A. Of the 3 haplotypes, *ADH7*-ht1 and *ADH7*-ht2 were excluded from the analysis as they were almost identical, with rs3737482T>C and rs1154460G>A, respectively. The *ADH7*-ht3 haplotype (T allele in rs3737482 and G allele in rs1154460) was analyzed.

In the genetic analysis of *ADH7* ht3, the ht3 -/- group was 62.0% in the case group and 67.1% in the control group. The ht3 +/- group was 34.0% in the case group and 29.8% in the control group. The ht3 +/+ group was 4.0% in the case group and 3.1% in the control group. Based on the ht3 -/- group, the OR of the ht3 +/- group was 1.22(95% CI: 0.77–1.93) and 0.99(95% CI: 0.55–1.78) in the ht3 +/- group, and no statistically significant difference was found (Table 4).

### *ADH7* rs3737482T>C and rs1154460G>A and risk of head and neck squamous cell carcinoma according to alcohol consumption

The relative risk of HNSCC was analyzed in *ADH7* rs3737482T>C and rs1154460G>A, according to alcohol drinking history. In *ADH7* rs3737482T>C, based on the TT genotype, the OR was 0.43 (95% CI: 0.42–0.77) in the CT genotype and 0.42 (95% CI: 0.19–0.94) in the CT genotype in the drinker group, indicating a significant decrease. In *ADH7* rs1154460G>A, based on the GG genotype, the OR of the AA genotype were 3.55 (95% CI: 1.51–8.33) in the drinker group, indicating a significant increase (Table 5). The analysis was also performed by dividing the drinker group into social drinkers and heavy drinkers. In *ADH7* rs3737482T>C, based on the TT genotype, the OR was 0.16 (95% CI: 0.04–0.69) in the CC genotype in the social drinker group and 0.40 (95% CI: 0.17–0.92) in the CT genotype in the heavy-drinker group. In *ADH7* rs1154460G>A, based on the GG genotype, the OR of the AG genotype and the AA genotype were 2.60 (95% CI: 1.02–6.62) and 5.85 (95% CI: 1.58–21.62) in the social drinker group.

## Discussion

In terms of *ADH7* SNPs in head and neck cancer, *ADH7* rs1573496 SNP was most commonly investigated. Several studies analyzed the relationship between the *ADH7* rs1573496 SNP and the risk of HNSCC [19-25]. However, conflicting results are found regarding the relationship between the *ADH7* rs1573496 SNP and the risk of HNSCC among previous studies. Hashibe et al. analyzed 3,800 patients with malignant tumors of the upper aerodigestive tract, including esophageal cancer, and 5,200 of the control group from three multi-center data in Europe and Latin America. They reported that the CC genotype of *ADH7* rs1573496C>G exhibits an OR of 0.68 (95% CI: 0.60–0.78), showing a protective effect against cancer [24]. Wei et al. performed a case-control study on 1,110 patients with HNSCC and 1,129 controls in non-Hispanic white Americans. They reported that the OR of the GG genotype in *ADH7* rs1573496C>G was 0.32 (95% CI: 0.13–0.82), and the OR of CG+GG genotype was 0.74 (95% CI: 0.59–0.94), indicating a decreased risk of head and neck cancer [20].

However, some studies failed to detect any significant correlation between *ADH7* rs1573496 SNP and the risk of HNSCC. Hakenwerth et al. reported that *ADH7* rs1573496 SNP did not show a clear relationship with head and neck cancer risk in European-American and African-American patients with HNSCC [21]. Also, another study conducted in Japan using 585 patients with head and neck cancer and 1,170 controls reported that *ADH7* rs1573496 SNP comprised of all homozygous C alleles, and further analysis was not possible [22]. Also, the other study conducted in India to evaluate the relationship between oral cancer and alcohol metabolism revealed the rarity of *ADH7* rs1573496 in the Indian population [23]. In the current study, all HNSCC patients showed CC homozygous in *ADH7* rs1573496C>G, and only one patient in the control group exhibited the CG genotype. Therefore, performing further analysis was not possible. These results suggest that the frequencies of the alleles and SNP genotypes of *ADH7* rs1573496 vary by different ethnic groups.

About *ADH7* rs1154460G>A, previous studies showed differences based on ethnicity. Hakenwerth et al. reported that *ADH7* rs1154460G>A SNP did not show a clear relationship with head and neck cancer risk in European-American and African-American patients with HNSCC [21]. This is in contrast to the study that investigated this allele and found it to be associated with an increased OR in Japanese populations [22]. In the current study, *ADH7* rs1154460G>A SNP was associated with an increased risk of head and neck cancer.

Regarding *ADH7* rs3737482T>C and rs284787T>C SNPs in head and neck cancer, the results of the current study were similar to those of a previous study conducted by Oze et al., confirming the association with the risk of head and neck cancer [22]. Oze et al. reported that *ADH7* rs3737482T>C SNP results in an independent and significant effect on decreasing the risk of head and neck cancer [22]. Also, in the current study, *ADH7* rs3737482T>C SNP was associated with decreased risk of head and neck cancer. Regarding *ADH7* rs284787T>C SNP, Oze et al. showed no statistically significant result [22]. Also, in this study, it was not associated with the risk of HNSCC.

Determining the effects of individual polymorphism on cancer is not easy because all ADH genes are in one cluster, and linkage disequilibrium exists. Recent multi-center research conducted by Hashibe et al. using HapMap analysis suggested that *ADH1A*, *ADH1B*, *ADH1C*, *ADH4*, *ADH5*, and *ADH6* exhibit a relatively high linkage disequilibrium, but *ADH7* exhibit relatively smaller linkage disequilibrium compared to the other 6 types [24].

Linkage disequilibrium (LD) in gene analysis is a statistically inconsistent condition in which the frequencies present at two different genetic loci with the theoretical value that exists under the assumption that the two genetic loci are independent and not associated with each other in the group, meaning they act as if they are related, regardless of whether or not they are the same gene.

Haplotype refers to a combination of series of SNPs that exists close to each other on one gene. They appear as a bundle, not independently but statistically associated with each other on one gene. It is easy to get information about the association of nucleotide polymorphism combinations; therefore, detailed information could be found compared to studying individual SNPs.

In this study, the haplotype results showed no independent association with HNSCC risk. This might be due to the effects of the strong linkage disequilibrium between *ADH7* rs3737482 and rs1154460 SNPs.

The possible interaction between environmental factors and the genetic susceptibility for cancer has been suggested. Hakenewerth et al. reported a synergistic interaction between alcohol consumption and genetic polymorphism in head and neck cancer development [21]. In the current study, we analyzed HNSCC risk changes in *ADH7* rs3737482T>C and rs1154460G>A SNPs, according to alcohol consumption, to evaluate the interaction between genetic polymorphism and environmental factors. No statistically significant interaction was found in both SNPs in the non-drinker group. However, in the drinker group, the OR of rs3737482T>C decreased significantly, and the OR of rs1154460G>A increased significantly. These results might support a synergistic interaction between the environmental factor of alcohol consumption and the genetic factor of *ADH7* SNP. However, the OR did not increase in proportion to the alcohol consumption in the social or heavy-drinker groups. A small sample size might be related to these heterogeneous results. Also, one study that investigated the association between five *ADH1B-ADH1C-ADH7* cluster SNPs and the risk of developing esophageal squamous cell carcinoma in the Chinese population did not show any significant gene-drinking interaction [26]. Therefore, further studies with large sample sizes in different ethnic groups may be necessary to clarify the effect of the interaction between *ADH7* SNPs and alcohol consumption on the risk of HNSCC. Also, investigating enzyme function and activity according to SNPs and alcohol consumption is necessary.

The current study exhibits some limitations. First, it was a hospital-based case-control study; the control group was made up of non-cancer patients who visited the hospital. Therefore, an evitable bias and question exists; whether the gene frequency of the control group could represent the general population, although the genotype frequencies did not deviate from the Hardy-Weinberg equilibrium in the control group. Second, the sample size of the study might be relatively small to reach a firm conclusion. Third, a significant difference was found in the mean age between the case and control groups. It might influence the study results, although the OR was analyzed with adjustment for age. Further studies with large sample sizes and age-matched samples would have more strength and allow for better risk estimation.

Despite those limitations, it might be notable that this study is the first study that analyzed the four SNPs of *ADH7* and their relationship with the risk of developing HNSCC in Koreans.

## Conclusion

Based on the results of the current study, SNPs of *ADH7* rs3737482T>C and *ADH7* rs1154460G>A are associated with the risk of development of head and neck squamous cell carcinoma in Koreans and could be potentially useful molecular biological markers for identifying individuals at high risk of developing HNSCC. Furthermore, SNPs of *ADH7* rs3737482T>C and *ADH7* rs1154460G>A exhibit synergistic interactions with alcohol composition on the risk of HNSCC.

## Declarations

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Conflicts of interest/Competing interests

Not applicable

### Availability of data and material (data transparency)

Not applicable

### Code availability (software application or custom code)

Not applicable

### Authors' contributions

Dong Won Lee was involved in the study's design, data acquisition, analysis, interpretation, initial draft, and critical revision of the manuscript. Yong Bae Ji, Chang Myeon Song, Jeong Kyu Kim, and Seung Hwan Lee were involved in data analysis, interpretation, and critical revision of the manuscript. Kyung Tae was involved in the conception and design of the work, interpretation, critical revision of the manuscript, and accountability for all aspects of the work. All authors have read and approved the final manuscript.

### Ethics approval

Ethical approval was granted as indicated in the article.

### Informed consent

Informed consent was obtained from all individual participants included in the study.

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## Tables

Table 1  
Primer sequence for ADH7 single nucleotide polymorphism genotyping.

Gene	Locus	Primer name	Primer sequence
ADH7	rs1573496_CG	rs1573496_CG_F	TCGCTCCTAATGCAAAGGTT
		rs1573496_CG_R	CAGATTTTGGCCACAGGAAT
		rs1573496_CG_AM21	CCTGGTTTCACTGTAGTCACT
	rs3737482_TC	rs3737482_TC_F	TCGCTCCTAATGCAAAGGTT
		rs3737482_TC_R	CAGATTTTGGCCACAGGAAT
		rs3737482_TC_AM27	TCTAAGGTTTATAAACACCGTAAGGTT
	rs1154460_GA	rs1154460_GA_F	TTTGGTCCAGTGAACCTGCT
		rs1154460_GA_R	ATTGGGCATCTTGAAACCAT
		rs1154460_GA_AM38	ATAATAAAGTTATAGACAATTAAATTTACCTTGTGCAT
	rs284787_TC	rs284787_TC_F	ACAAGGCTATTTGCCAGCAT
		rs284788_TC_R	AAAAACACTTTTTATTAAATGGAGTCA
		rs284789_TC_AM32	TGTTCAATTTGATACAGTAGAATTGCAAGTCC

Table 2  
Single nucleotide polymorphism and allele frequencies of ADH7 in Korean head and neck squamous cell carcinoma patients and controls.

Gene	Locus	Amino acid change	Genotype				Frequency	HWE*
ADH7	rs1573496C > G	Gly92Ala	C	CG	G	N	0.001	0.983
			571	1	0	572		
	rs3737482T > C		T	CT	C	N	0.451	0.783
			174	280	118	572		
	rs1154460G > A		G	AG	A	N	0.356	0.177
			230	277	65	572		
	rs284787T > C		T	CT	C	N	0.344	0.690
			248	254	70	572		

\* *p* value for deviation from Hardy-Weinberg Equilibrium

Table 3

Logistic analysis of ADH7 single nucleotide polymorphisms in Korean head and neck squamous cell carcinoma patients and controls.

Gene	Loci	Genotype	Distribution		Referent analysis		Codominant analysis		Dominant analysis		Recessive analysis	
			Case (%)	Control (%)	OR* (95% CI†)	P	OR(95% CI)	P	OR(95% CI)	P	OR(95% CI)	P
ADH7	rs1573496C >G	CC	250(100.0)	321(99.7)	1							
		CG	0(0.0)	1(0.3)	.	.						
		GG	0(0.0)	0(0.0)	.	.						
	rs3737482T >C	TT	93(37.2)	81(25.2)	1							
		CT	111(44.4)	169(52.5)	0.48(0.29–0.78)	0.003	0.66(0.49–0.90)	0.008	0.47(0.30–0.75)	0.002	0.76(0.44–1.29)	0.31
		CC	46(18.4)	72(22.4)	0.69(0.49–0.96)	0.03						
	rs1154460G >A	GG	94(37.6)	136(42.2)	1							
		AG	120(48.0)	157(48.8)	1.31(0.83–2.06)	0.25	1.47(1.06–2.04)	0.02	1.49(0.96–2.32)	0.08	2.03(1.05–3.92)	0.04
		AA	36(14.4)	29(9.0)	1.63(1.11–2.40)	0.01						
	rs284787T >C	TT	101(40.4)	147(45.7)	1							
		CT	118(47.2)	136(42.2)	1.43(0.90–2.28)	0.13	1.32(0.97–1.80)	0.08	1.47(0.95–2.28)	0.08	1.38(0.74–2.58)	0.32
		CC	31(12.4)	39(12.1)	1.24(0.87–1.74)	0.23						

\* adjusted Odds ratio; †95% Confidence interval

Table 4

Analysis of haplotypes of ADH7 in Korean head and neck squamous cell carcinoma patients and controls.

Gene	Loci	Geno type	Distribution		Referent analysis		Codominant analysis		Dominant analysis		Recessive analysis	
			Case (%)	Control (%)	OR* (95% CI†)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	P
ADH7	ht3	-/-	155 (62.0)	216 (67.1)	1							
		ht3/-	85 (34.0)	96 (29.8)	1.22 (0.77–1.93)	0.40	1.12 (0.77–1.65)	0.55	1.19 (0.76–1.86)	0.45	0.91 (0.29–2.87)	0.88
		ht3/ht3	10 (4.0)	10 (3.1)	0.99 (0.55–1.78)	0.97						

\* adjusted Odds ratio; †95% Confidence interval

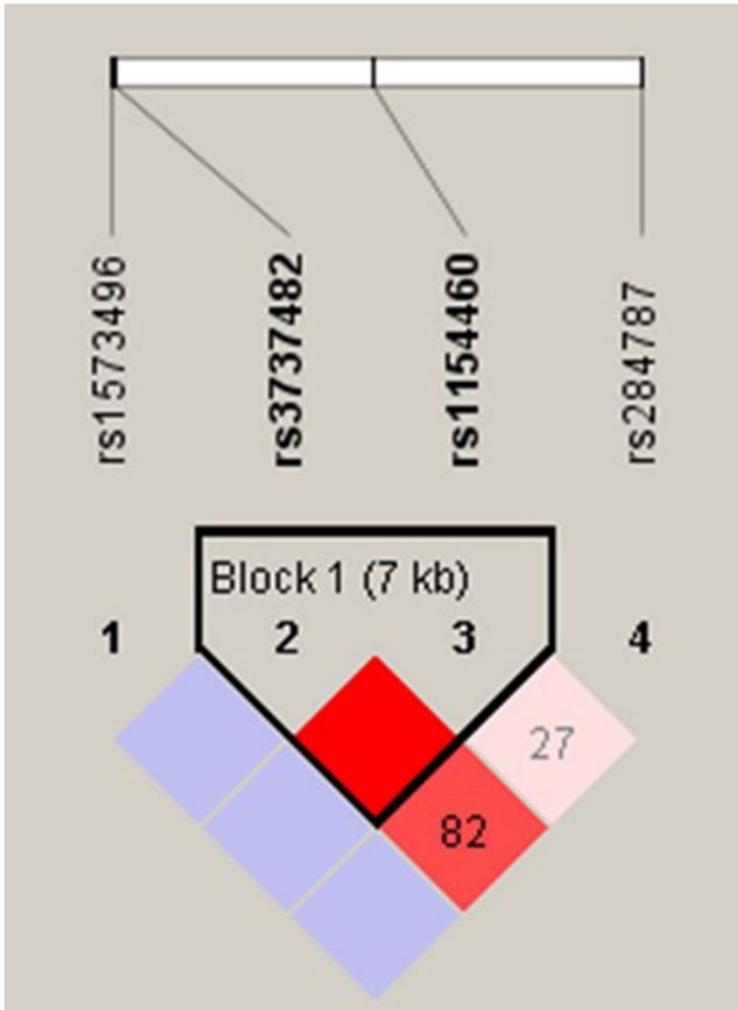
Table 5

Logistic analysis of ADH7 rs3737482T > C and rs1154460G > A polymorphism in Korean head and neck squamous cell carcinoma patients and controls according to alcohol consumption.

Gene	Alcohol	Genotype	Cancer	Normal	OR* (95% CI†)	P
ADH7 rs3737482T > C	Non-drinker (n = 182)	TT	26 (28.0 %)	21 (23.6 %)	1	
		CT	44 (47.3 %)	42 (47.2 %)	0.59 (0.21–1.68)	0.322
		CC	23 (24.7 %)	26 (29.2 %)	0.75 (0.23–2.42)	0.628
	Drinker (n = 390)	TT	67 (42.7 %)	60 (25.8 %)	1	
		CT	67 (42.7 %)	127 (54.5 %)	0.43 (0.42–0.77)	0.004
		CC	23 (14.6 %)	46 (19.7 %)	0.42 (0.19–0.94)	0.034
ADH7 rs1154460G > A	Non-drinker (n = 182)	GG	43 (46.2)	41 (46.1)	1	
		AG	39 (41.9)	39 (43.8)	0.80 (0.32–2.01)	0.631
		AA	11 (11.8)	9 (10.1)	1.25 (0.30–5.27)	0.760
	Drinker (n = 390)	GG	51 (32.5 %)	95 (40.8 %)	1	
		AG	81 (51.6 %)	118 (50.6 %)	1.55 (0.87–2.75)	0.136
		AA	25 (15.9 %)	20 (8.6 %)	3.55 (1.51–8.33)	0.004

\* adjusted Odds ratio; †95% Confidence interval

## Figures



**Figure 1**  
 Gene structure and linkage disequilibrium of genotyped single nucleotide polymorphisms (SNPs) of AHD7. Linkage disequilibrium is displayed using Haploview. D' values are given in the rhombus cell intersecting for each pair of SNPs. A blank cell indicates D' = 1.0. The darker the cell, the greater the linkage disequilibrium between the SNPs. Haplotype blocks are outlined.