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Diagnostic Impacts of Aldehyde Dehydrogenase 2 Genetic Variants on Hepatocellular Carcinoma Susceptibility

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Abstract. *Background/Aim: The role of alcohol consumption and aldehyde dehydrogenase 2 (ALDH2) genotype in hepatocellular carcinoma (HCC) development remains uncertain. Materials and Methods: We conducted genotyping of the ALDH2 rs671 single nucleotide polymorphism in 298 patients with HCC and 889 non-cancerous healthy controls. We assessed associations stratified by sex and alcohol consumption status. Results: Distribution of ALDH2 rs671 variant genotypes differed significantly between HCC patients and controls (p_{trend}=0.0311). Logistic regression analyses indicated that compared to the wild-type GG genotype, the heterozygous variant AG genotype and homozygous variant AA genotype conferred 1.22- and 1.77-fold increases in HCC risk (p=0.1794 and 0.0150, respectively). Allelic frequency analysis showed that the A allele was associated with a 1.29-fold increased HCC risk (p=0.0123). Additionally, AA genotype carriers had significantly higher HCC risk than GG genotype carriers among males (p=0.0145) and non-alcohol drinkers (p<0.001). Conclusion: HCC risk is influenced by ALDH2 genotype, with effects modified by sex and alcohol consumption. Particularly, individuals with the ALDH2 rs671 AA genotype should avoid alcohol consumption, especially males.*

Hepatocellular carcinoma (HCC) ranks sixth in global cancer prevalence and third in cancer-related mortality (1-3). Despite significant advancements in systematic therapies for HCC, including targeted therapy, immune checkpoint inhibitors, and intravenous chemotherapy, the 5-year recurrence rate remains high at 75% (4, 5). HCC represents a formidable global public health challenge (6). Recently, genome-wide (7, 8) and candidate gene studies (9-12), have revealed several potential diagnostic biomarkers for HCC. Nevertheless, identifying a clinically validated diagnostic marker remains challenging (13).

Aldehyde dehydrogenase 2 (ALDH2) is known for its role in ethanol metabolism, primarily expressed in liver mitochondria where it catalyzes the conversion of toxic acetaldehyde to acetic acid. Numerous studies have investigated associations between *ALDH2* genotypes and various human diseases, including coronary artery stenosis (14), myocardial infarction (15), and ischemic stroke (16). Among single nucleotide polymorphisms (SNPs), *ALDH2* rs671 is the most extensively studied, incorporating rs60823674, rs4986830, rs4134524, and rs2230021. Individuals carrying at least

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Key Words: Alcohol drinking, aldehyde dehydrogenase 2 (ALDH2), genotype, hepatocellular carcinoma, polymorphism.

Table I. *Summary of selected characteristic data of the 298 patients with hepatocellular carcinoma and the matched 889 healthy controls.*

Characteristic	Controls (n=889)			Cases (n=298)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			55.4 (4.9)			52.3 (4.5)	0.7418
Sex							
Male	636	71.5%		213	71.5%		0.9830
Female	253	28.5%		85	28.5%		
Personal habits							
Smoking							
Ever smokers	579	65.1%		224	75.2%		0.0017*
Never smokers	310	34.9%		75	14.8%		
Alcoholism							
Ever drinkers	518	41.7%		206	69.1%		0.0011*
Never drinkers	371	58.3%		92	30.9%		

SD: Standard deviation; [a]based on Student's *t*-test and Chi-square test properly. *Statistically significant, $p<0.05$.

one variant allele of *ALDH2* rs671 demonstrate significantly reduced enzymatic activity (17, 18), leading to heightened sensitivity to alcohol, commonly referred to as "Asian Flush Syndrome" (19-21). Moreover, the AA genotype of *ALDH2* rs671 has been linked to increased risks of upper digestive tract cancers and head and neck cancers (22, 23). Furthermore, *ALDH2* polymorphisms influence HCC development in non-alcoholic patients (24, 25).

In the literature, several studies have indicated that the *ALDH2* rs671 polymorphism does not correlate with HCC susceptibility in East Asian populations (26-29). Nevertheless, the influence of alcohol consumption patterns and *ALDH2* rs671 genotypes on HCC development remains uncertain and warrants further investigation. Thus, our study aimed to explore the association between *ALDH2* rs671 genotypes and the combined impact of alcohol drinking behaviors with *ALDH2* rs671 genotypes on HCC risk in a representative Taiwanese population, comprising 298 HCC cases and 889 non-cancerous healthy controls.

Materials and Methods

Recruitment of HCC patients and non-cancerous control groups. Patients diagnosed with HCC by expert surgeons at China Medical University Hospital, Taiwan, were eligible for recruitment. HCC patients and non-cancerous healthy subjects who consented to complete a self-administered questionnaire and provided peripheral blood samples were enrolled in the study. Non-cancerous healthy controls, matched for age and sex, were selected from the Health Examination Cohort during the same period. The study design, including exclusion and inclusion criteria, was approved by the Institutional Review Board of China Medical University Hospital (DMR103-IRB-094). Table I summarizes selected information extracted from the questionnaire database of HCC cases and non-cancerous healthy subjects.

Genotyping methodology for ALDH2 rs671 polymorphism. Peripheral blood leukocytes from each participant were isolated using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan, ROC), following procedures described in previous publications (30-32). PCR amplification of the *ALDH2* rs671 polymorphic site was performed using specific primers: forward 5'-CAA ATT ACA GGG TCA ACT GC-3' and reverse 5'-CCA CAC TCA CAG TTT TCT CTT-3', followed by genotyping using PCR-restriction fragment length polymorphism analysis. Genotypic processing was independently conducted by trained researchers (Chang WS, Tsai CW, Wang YC, Shih HY, and Chin YT) in a double-blind manner. All repeated genotyping results were 100% concordant. The physical map illustrating the locations of *ALDH2* rs671 is presented in Figure 1.

Statistical methodology. Statistical analyses were conducted using SPSS version 16.0 software (SPSS, Inc., Chicago, IL, USA). The goodness-of-fit chi-square test assessed the Hardy-Weinberg equilibrium in the non-cancerous control group. The differential distributions of age between the HCC case and non-cancerous control groups were evaluated using Student's *t*-test. Pearson's chi-squared test with Yates' correction examined the differential distribution of various *ALDH2* genotypes and alleles. Associations between *ALDH2* genotypes and HCC risk, as well as the combined impacts of *ALDH2* genotypes with sex or alcoholism, were assessed through multivariable logistic regression analyses, calculating odds ratios (ORs) and corresponding 95% confidence intervals (CIs). A probability value ≤ 0.05 was considered statistically significant.

Results

The demographic data for the HCC populations. Table I presents the demographic characteristics including age, sex, smoking status, and alcohol consumption habits of the study participants, comprising 298 HCC patients and 889 non-cancerous healthy subjects. Utilizing a matching strategy ensured comparable age and sex distributions between cases and controls (both $p>0.05$) (Table I). The case group

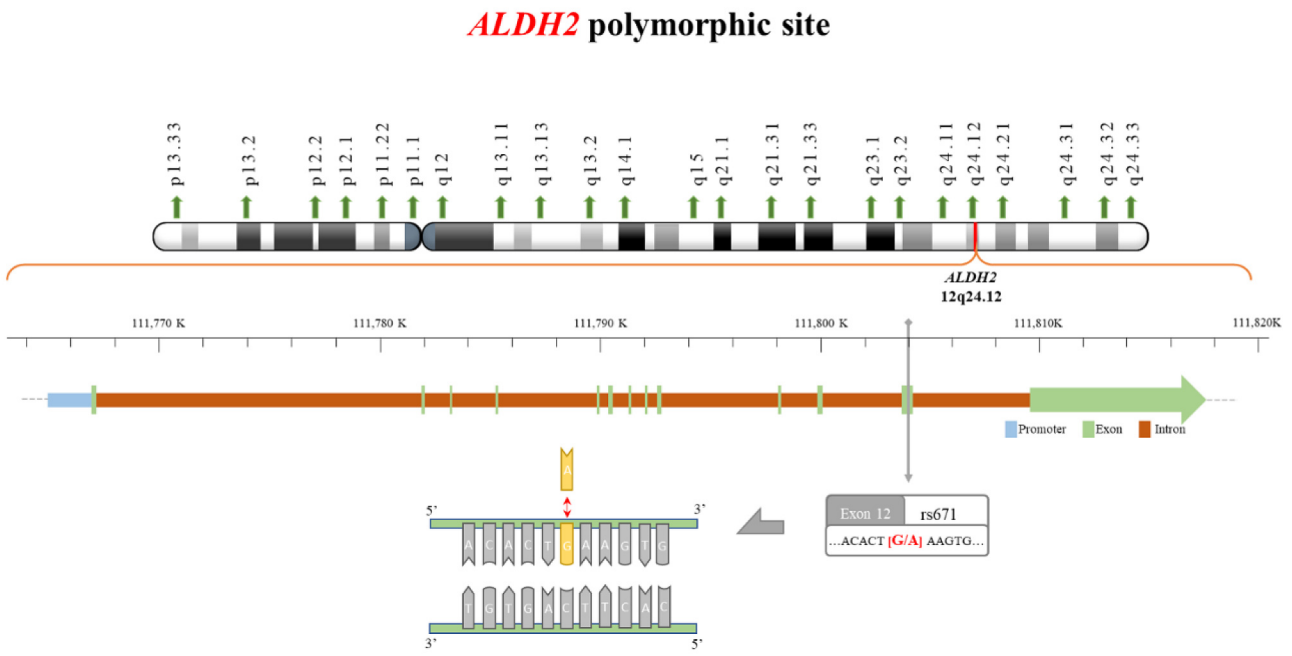

Figure 1. *The physical map of polymorphic site for ALDH2 rs671 on chromosome 12.*

exhibited significantly higher proportions of ever smokers and ever alcohol drinkers compared to the control group (75.2% *vs*. 65.1% and 69.1% *vs*. 41.7%, respectively; p=0.0017 and 0.0011) (Table I). These results underscore the role of individual cigarette smoking and alcohol consumption as risk factors for HCC in Taiwan.

Associations of ALDH2 genotypes with HCC risk. Table II displays the distributions of *ALDH2* rs671 genotypes among HCC cases and non-cancerous healthy controls. First, genotypic frequencies of the SNP in non-cancerous healthy controls were consistent with Hardy-Weinberg equilibrium (p_{HWE}=0.8512). Second, *ALDH2* rs671 genotype frequencies differed significantly between HCC cases and healthy controls, with higher proportions of the heterozygous variant AG and homozygous variant AA genotypes observed in HCC cases compared to controls (43.6% *vs*. 41.2% for AG and 12.4% *vs*. 8.1% for AA genotype, p_{trend}=0.0311). Logistic regression analyses revealed that the AA genotype was associated with an increased risk of HCC [odds ratio (OR)=1.77, 95% confidence interval (95%CI)=1.38-2.75, p=0.0150] relative to the wild-type GG genotype. In a dominant model analysis, individuals carrying variant genotypes (AG+AA) exhibited a 1.31-fold increased HCC risk (95%CI=1.01-1.71, p=0.0504, Table II).

Contributions of ALDH2 allelic frequencies to HCC risk. Table III presents the allelic frequencies of *ALDH2* rs671

Table II. *Genotypic frequency distributions of ALDH2 rs671 among the 298 hepatocellular carcinoma cases and 889 non-cancerous healthy controls.*

Genotypes	Controls, n (%)	Cases, n (%)	OR (95%CI)	p-Value[a]
rs671				
GG	451 (50.7)	131 (44.0)	1.00 (Reference)	
AG	366 (41.2)	130 (43.6)	1.22 (0.93-1.62)	0.1794
AA	72 (8.1)	37 (12.4)	1.77 (1.38-2.75)	0.0150*
AG+AA	438 (49.3)	167 (56.0)	1.31 (1.01-1.71)	0.0504
P_{trend}				0.0311*
P_{HWE}				0.8512

OR: Odds ratio; CI: confidence interval; [a]Data based on Chi-square test with Yates' correction; p_{trend}: p-value based on trend analysis; p_{HWE}: p-value based on Hardy-Weinberg Equilibrium; *Statistically significant.

Table III. *Allelic frequencies for ALDH2 rs671 polymorphisms among the hepatocellular carcinoma cases and non-cancerous healthy controls.*

Genotypes	Controls, n (%)	Cases, n (%)	OR (95%CI)	p-Value[a]
rs671				
Allele G	1268 (71.3)	392 (65.8)	1.00 (Reference)	
Allele A	510 (28.7)	204 (34.2)	1.29 (1.06-1.58)	0.0123*

OR: Odds ratio; CI: confidence internal; [a]Data based on Chi-square test with Yates' correction; *Statistically significant.

Table IV. *Distribution of ALDH2 rs671 genotypes among hepatocellular carcinoma cases and non-cancerous controls after stratification by sex.*

Genotype	Males, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value	Females, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
GG	323	90	1.00 (ref)	1.00 (ref)		128	41	1.00 (ref)	1.00 (ref)	
AG	257	93	1.30 (0.93-1.81)	1.42 (0.89-1.88)	0.1455	109	37	1.05 (0.63-1.77)	1.11 (0.59-1.68)	0.9275
AA	56	30	**1.92 (1.16-3.17)**	**2.12 (1.37-3.48)**	**0.0145**	16	7	1.37 (0.53-3.55)	1.46 (0.49-3.90)	0.7003
Total	636	213				253	85			
p_{trend}					**0.0275**					0.8125

N: Number; OR: odds ratio; CI: confidence interval; [a]Based on Chi-square with Yate's correction test; [b]Based on Chi-square with Yate's correction test after adjustment of age, cigarette smoking and alcohol drinking status. Statistically significant outcomes are shown in bold.

Table V. *Distribution of ALDH2 rs671 genotypes among hepatocellular carcinoma cases and non-cancerous controls after stratification by alcoholism status.*

Genotype	Never drinkers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value	Ever drinkers, N		OR (95%CI)[a]	aOR (95%CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
GG	197	38	1.00 (ref)	1.00 (ref)		254	93	1.00 (ref)	1.00 (ref)	
AG	162	36	1.15 (0.70-1.90)	1.20 (0.73-1.78)	0.6702	204	94	1.26 (0.90-1.77)	1.38 (0.96-1.69)	0.2163
AA	12	18	**7.62 (3.39-17.11)**	**6.43 (2.71-9.86)**	**0.0001**	60	19	0.86 (0.49-1.53)	0.82 (0.44-2.17)	0.7191
Total	371	92				518	206			
p_{trend}					**7.9E-8**					0.2704

N: Number; OR: odds ratio; CI: Confidence interval; [a]Based on Chi-square with Yate's correction test; [b]Based on Chi-square with Yate's correction test after adjustment of age, sex, and cigarette smoking status. Statistically significant outcomes are shown in bold.

among HCC cases and non-cancerous healthy controls. Consistent with the results from Table II, individuals carrying the variant A allele of *ALDH2* rs671 exhibited a higher risk of HCC compared to those with the wild-type G allele (OR=1.29, 95%CI=1.06-1.58, p=0.0123, Table III).

Stratified analysis of ALDH2 rs671 genotypes based on sex and alcohol drinking status. We attempted to investigate the combined impact of *ALDH2* rs671 genotype with sex and alcohol consumption on HCC risk. Regarding sex, a significant interaction was observed between *ALDH2* rs671 genotype and males (p_{trend}=0.0275), particularly among those carrying the AA genotype (p=0.0145, left part of Table IV). Conversely, no significant interaction was found between genotype and females, whether individuals were AG or AA carriers (p=0.9275 and 0.7003, right part of Table IV). This pattern persisted after adjusting for age, smoking, and alcohol consumption status (Table IV).

Regarding alcohol consumption status, a significant interaction was noted between *ALDH2* rs671 genotype and non-drinkers (p_{trend}=7.9E-8), particularly among those with the AA genotype (p=0.0001, left part of Table V). Conversely, there was no significant interaction between *ALDH2* rs671 genotype and drinkers, whether individuals carried AG or AA genotypes (p=0.2163 and 0.7191, right part of Table V). Adjusting for age, sex, and smoking status reaffirmed these findings (Table V).

Discussion

In the current study, we explored the role of alcohol consuming status and *ALDH2* genotype in HCC development. The *ALDH2* rs671 genotype is prevalent in East Asian populations, with frequencies ranging from 28-45%, contrasting its rarity in Western populations (33). Some studies suggest that carriers of the variant *ALDH2* rs671 genotypes may self-select against alcohol consumption due to the acetaldehyde-induced flushing reaction (20, 21). However, recent trends indicate increasing alcohol consumption among East Asian populations (34), potentially contributing to elevated HCC risk (35, 36).

Our study highlights that the variant AA genotypes of *ALDH2* rs671 are associated with increased HCC risk, particularly among males (Table II, Table III, and Table IV). Furthermore, the *ALDH2* rs671 AA genotype significantly enhances HCC risk among non-alcohol drinkers (Table V, left part). These findings contrast with previous reports suggesting inconsistent associations between *ALDH2* rs671 polymorphism and HCC risk in alcohol drinkers (37-40).

Of particular interest, our study suggests that the AA genotype of ALDH2 rs671 may lead to severe consequences for alcohol drinkers, potentially resulting in a biased OR estimate (Table V, right part). Conversely, the pronounced effects of the ALDH2 rs671 AA genotype among non-drinkers are evident (Table V, left part), potentially obscuring the inclusion of HCC cases with *ALDH2* rs671 AA genotype who were alcohol drinkers and did not survive to be included in our study sample.

In the literature, the *ALDH2* rs671 polymorphism has been reported to be associated with HCC risk among patients without alcoholism (24, 25). This finding is consistent with our observation that among non-drinkers, carriers of the AA genotype at *ALDH2* rs671 had a 7.6-fold increased OR for HCC risk (Table V, left part). However, a meta-analysis indicated that the *ALDH2* rs671 polymorphism is not generally associated with HCC susceptibility in East Asian patients with HBV or hepatitis C virus (26). Furthermore, several studies have shown that the *ALDH2* rs671 polymorphism is not associated with HCC in East Asian populations (26-29). These discrepancies may stem from differences in study designs that consider virus infections (26, 28), or variations in the studied populations such as Japanese, distinct from the Han Chinese population examined in our study (27, 29).

This study was conducted in a homogeneous cohort of HCC patients of Han Chinese descent, characterized by a significantly higher frequency of the *ALDH2* rs671 "A" allele compared to other populations, as demonstrated in the 1000Genomes Project. Specifically, the *ALDH2* rs671 "A" allele frequencies were nearly 0% in African, American, European, and South Asian populations, whereas they were 25.5% in East Asian populations with a sample size of 3,118 subjects (41). Consequently, it is crucial to emphasize that the predictive implications of this study are applicable primarily to East Asian populations. The combined effects of the *ALDH2* rs671 genotype with alcohol consumption could not be broadly extrapolated to other populations.

Conclusion

This study provides evidence that variant genotypes at *ALDH2* rs671 are associated with increased HCC risk, especially among males. Furthermore, these genotypes significantly elevate HCC risk among non-alcohol drinkers and may have severe consequences for alcohol drinkers. *ALDH2* rs671 serves not only as a genetic susceptibility locus for HCC in Taiwanese populations but also as a critical predictor for potential life-threatening outcomes. Individuals carrying the *ALDH2* rs671 A-allele, particularly those with the AA genotype, are advised to discontinue alcohol consumption promptly.

Conflicts of Interest

All the Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Conceptualization: Chin YT, Wu MH and Bau DT; Data curation: Wu MH, Pei JS, Ke TW and Hung YC; Investigation: Wu MH, Shih HY, Tsai CW, Wang YC and Chang WS; Formal analysis: Pei JS, Chen JC and Chang WS; Writing – original draft: Chang WS and Bau DT; Writing – review & editing: Chin YT, Wu MH, Shih HY, Tsai CW, Pei JS, Ke TW, Wang YC, Hung YC, Chen JC, Bau DT and Chang WS.

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