Role of ALDH2 in Hepatic Disorders: Gene Polymorphism and Disease Pathogenesis

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Abstract

Aldehyde dehydrogenase 2 (ALDH2) is a key enzyme of alcohol metabolism and it is involved in the cellular mechanism of alcohol liver disease. ALDH2 gene mutations exist in about 8% of the world’s population, with the incidence reaching 45% in East Asia. The mutations will result in impairment of enzyme activity and accumulation of acetaldehyde, facilitating the progression of other liver diseases, including non-alcoholic fatty liver diseases, viral hepatitis and hepatocellular carcinoma, through adduct formation and inflammatory responses. In this review, we seek to summarize recent research progress on the correlation between ALDH2 gene polymorphism and multiple liver diseases, with an attempt to provide clues for better understanding of the disease mechanism and for strategy making.

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Introduction of gene polymorphisms in aldehyde dehydrogenase 2

Function of aldehyde dehydrogenase 2 in human beings

The aldehyde dehydrogenases play a key role in the metabolism of toxic aldehydes. Some are produced in human bodies, such as 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA), while others are obtained from the environment, like formaldehyde, acrolein, and ethyl.1,2 As a member of the ALDH superfamily, ALDH2 is the most sensitive isoform to irreversible inactivation and is also the most sensitive to inactivation by toxins, such as 4-HNE.1 This enzyme could metabolize acetaldehyde (ACH) to acetate irreversibly in a redox reaction (Fig. 1).3 Disturbances in the expression of ALDH2 will dampen its metabolic capacity and result in accumulation of ACH consequently. Based on its electrophilic feature, ACH could bind with biomolecules such as proteins or DNA and destroy cell integrity, which contributes to the development of various human diseases,4 such as endocrine disorders, cardiovascular diseases, pulmonary diseases, oral cancers, gastrointestinal cancers, Fanconi anemia, and dermatitis.5–7

ALDH2 gene and polymorphisms

ALDH2 is a polypeptide consisting of 517 amino acids, principally expressed in the liver but also in other organs, such as heart, kidney, muscle, and brain.8 Its coding gene is located on chromosome 12 (12q24.2), which is 44 kilobases in length and comprises 13 exons.2 After translation, the expressed protein is transported to the mitochondrial matrix to participate in dehydrogenase, esterase and reductase reactions in liver and fat tissues particularly. Studies of the human genome have shown 19 kinds of functional ALDH genes in total, with a wide range of expression and substrate specificities, among which the ALDH2 gene has the highest expression and exclusively harbors existence of genetic polymorphisms.1

As it encodes a key enzyme for alcohol metabolism, ALDH2 also has an important functional single nucleotide polymorphism (SNP), the rs671-Glu504Lys variant, which has significantly reduced activity compared to the wild type.10 The rs671 variant exists in 30–45% of East Asians (Chinese, Japanese, and Korean) and 8% of the world’s population.11,12 The incidence of this mutation in China is as high as 37–59%.13–16 Nowadays, the rs671SNP locus at exon 12 is of special concern in worldwide research. According to sequencing detection,17 a G→A point mutation is prone to occur at exon 12, causing the original glutamic acid (Glu) to be replaced by lysine (Lys), whose mutation is named ALDH2Glu504Lys (SNP rs671).

ALDH2rs671 SNPs are composed of three genotypes: GA, AA and GG. GA is a heterozygous mutation, also named as ALDH2*1/*2 (Glu/Lys). AA is a homozygous mutation, also known as ALDH2*2/*2 (Lys/Lys). GG is the normal allele, without mutation (Fig. 2). The majority of studies on these genotypes have confirmed that the GA genotype has 10–20% of the enzyme activity compared wild type, while the
AA genotype loses more than 96% of the enzymatic activity. As a result, individuals with GA or AA mutations could show up to 6 or 19 times greater ACH concentrations, respectively, as compared with wild type after alcohol intake.\(^{18}\)

**Distribution of ALDH2 alleles in different populations**

The genotype frequencies of the ALDH2 gene polymorphisms vary among different races. The rare ALDH2*2 allele has been observed in Caucasians, Africans and Southeast Asians but it is widely present in East Asians.\(^{19,20}\) There is a report of this mutation being found in about 560 million people of East Asian descent and reducing enzymatic activity by approximately 60% to 80% in ALDH2*1/*2 heterozygotes.\(^{18}\) Among East Asians, the ALDH2 allele frequencies are diverse among Japanese, Korean, and Chinese. In China, the ALDH2*2 gene frequency in some Chinese aboriginal populations (e.g., Korean, Uighur, Zhuang and Olunchun) is lower compared to the Chinese Han population. In the Chinese Han population, the ALDH2*2 allele frequency is 17% to 29%, the proportion of individuals with ALDH2*1/*2 heterozygotes is 36% to 44%, and the proportion of individuals with ALDH2*2/*2 homozygotes is 7% to 8%.\(^{21,22}\)

**Related liver diseases**

**Alcoholic liver disease**

Alcoholic liver disease (ALD) is a direct outcome of chronic ethanol consumption and is considered as an important health problem worldwide. ALD encompasses a broad spectrum of liver injuries, including steatosis, fibrosis, cirrhosis, and alcoholic hepatitis.\(^{23}\) The incidence of ALD has been increasing yearly because of the rapid boom in alcohol consumption in many developing countries over the past decade.\(^{24}\) The prevalence of ALD in China, the USA, Europe, and Japan is 4.5%, 6.2%, 6%, and 1.56–2.34%, respectively.\(^{25–27}\) There are about 260 million people occasionally, habitually and excessively drinking, and appropriately 2.5 million people die from ALD each year.\(^{28}\) Hence, ALD pathogenesis and therapy have always been the focus of national researchers.

The ALDH2 Glu504lys polymorphism is tied closely to occurrence and development of ALD in related individuals,\(^{29}\) though its polymorphism does not contribute to alcohol dependence in the Turkish population.\(^{30}\) Regardless of homozygous AA or heterozygous GA status, both guarantee elevated ACH level after alcohol drinking. A single-center study from the Fifth Medical Centre of the General Hospital of the Chinese People’s Liberation Army reported that only 2.3% of ALD patients have the ALDH2*2 allele, compared with 14.5% of the proportion of healthy controls (281 and 535 controls; odds ratio [OR] of 0.13 and 95% confidence interval [CI] of 0.07–0.24).\(^{31}\) In Korea, Lee et al.\(^{32}\) found that the ALDH2*1 allele is associated with a higher frequency of alcoholic cirrhosis (\(p=0.001\). Likewise, a meta-analysis of 12 studies found that people with the ALDH2*1 allele are more likely to go on to develop alcoholic liver cirrhosis compared with those with either the ALDH2*1/*2 or ALDH2*2/*2 genotype.\(^{33}\) Based on the activity of the enzyme after gene mutation, ALDH2*2/*2 should have produced a poor protective effect of ethanol; however, it brings some body information, such as facial flushing, reminding those with ALDH2*2/*2 to be alert to alcohol intake and usually leading to little excessive ethanol consumption.\(^{34}\) On the contrary, without the gene reminder, those with ALDH2*1 are not aware of consuming excessive alcohol.

The protection from the ALDH2 Glu504lys polymorphism has also been verified by Liu’s team,\(^{35}\) whose result demonstrated that individuals carrying this polymorphism are protected from alcohol drinking, with a 4-fold decrease in risk. Ma et al.\(^{36}\) and Li et al.\(^{16}\) also provided further evidence that...
the mutation and “alcohol flush” are not harmless in this Asian population. In other words, the ALDH2 gene mutation is a protective factor in the alcohol-drinking population in East Asia, while it is weaker in European and African populations. In fact, the Eastern culture encourages or challenges people to drink more alcohol in social activities, and sometimes people with flushing may not be able to escape or reject such alcoholism.

Aerobic glycolysis is involved in alcohol metabolism, which could be inhibited by a known factor: corticosterone. As is shown in the animal experiment of Gao’s team, a higher level of serum corticosterone is detected in ethanol-fed Aldh2−/− mice, compared to the wild type mice. Gao’s team also found that acute alcohol drinking in humans was related to elevated plasma glucocorticoid levels in human subjects, with higher levels in those with inactive ALDH2 than active ALDH2. To conclude, the progress of aerobic glycolysis is impaired by ethanol, especially in those with ALDH2*2. Meanwhile, they succeeded in restored canavanilin A-mediated hepatitis via blockade of corticosterone. Therefore, aerobic glycolysis-related signaling pathways may be a key factor. Interestingly, the authors found that glucose metabolism in T cells could be disrupted by ACH through inhibition of the aerobic glycolysis-related signal pathways. In addition, weakened autophagy is involved and compromised lysosomal activity will lead to abnormal stacking of ethanol or acetaldehyde by-product including protein or DNA adducts. Guo et al. reported that observations both in vivo and in vitro are in favor of a beneficial role of ALDH2 in alcohol intake-facilitated fatty liver and inflammation through autophagy regulation (Table 1).

The traditional hypothesized pathway is through oxidative stress. ALDH2 dramatically attenuates hepatic oxidative stress induced by chronic alcohol intake and favors a role of oxidative stress in ethanol- and ALDH2-elicted hepatic responses, by restoring autophagy and reopening autophagy flux. Additional ethanol consumption will increase the production of NADH/NAD+, and reactive oxygen species (ROS) in the mitochondrial electron transport chain. Then, ROS is able to activate nuclear factor-kappa B (NF-κB) and its downstream proinflammatory signal, and correspondingly aggravate inflammation and hepatocyte damage. Moreover, Zhong et al. selected mitochondrial ALDH2 as a promising therapeutic target for ALD. They said that it accelerates aldehyde clearance and reverses hepatic steatosis and apoptosis in mice. Therefore, artificial modulation of ALDH2 expression may be a potential therapeutic intervention for alcoholism and ALD in the future.

As mentioned above, variants in ALDH2 decrease the rate of ACH conversion to acetate because it blocks its ability to remove ACH and results in a strong aversive reaction. Therefore, if we can find a medium to intervene this mechanism and develop a blocker, we will alleviate this effect. It is also suggested that physicians should pay attention to explore the potential immunosuppressive therapy in alcoholics.

### Non-alcoholic fatty liver disease

It has become more and more accepted that non-alcoholic fatty liver disease (NAFLD) stands for not just a single type of liver disease but the hepatic manifestation of complicated metabolic dysfunctions. NAFLD covers a wide range of liver pathologies, including steatosis, steatohepatitis, fibrosis/cirrhosis and liver failure. Nowadays, NAFLD has become the leading cause of chronic liver diseases on earth and its global prevalence is appropriately 25%, 24.1%, 23.7%, 25%, 31% and 32% in China, the USA, Europe, Japan, the Middle East, and South America, respectively. In the USA, NAFLD is estimated to be the most common cause of chronic liver disease, affecting between 80 and 100 million individuals, among whom nearly 25% progress to non-alcoholic steatohepatitis. A recent report of data from the National Health and Nutrition Examination Survey ranging from 1988 to 2010 indicated that modest alcohol consumption (7–21 g/day) is associated with decreased mortality among patients with NAFLD. In contrast to the studies of 58,927 patients with NAFLD in Korea, even moderate drink-
Viral hepatitis

Although the global incidence of viral hepatitis, hepatitis B virus (HBV) infection mainly, is going down, it continues to play an important role in developing countries. There are approximately 257 million people with chronic HBV infection globally, including 68% in Africa and the Western Pacific, according to the World Health Organization report. In China, chronic hepatitis B (CHB) and chronic hepatitis C (CHC) affect 90 million and 10 million people, respectively. In developed countries such as the USA, Japan, and the European Union, the prevalence of HBV is much lower (0.71–1.17%), but the prevalence of hepatitis C virus (HCV) (1.10–1.56%) is higher than in China (HBV: 6.52%; HCV: 0.72%). In 2016, the Global Health Sector Strategy on viral hepatitis called for elimination of viral hepatitis as a major public health threat by 2030. However, unlike other liver diseases, the relationship between viral hepatitis and ALDH2 remains unclear.

HCV infection is an important cause of chronic liver disease, with nearly 71 million chronically infected people worldwide. HCV and alcohol intake are both risk factors for accelerated fibrosis progression, and alcohol use in the setting of HCV infection is correlated with increased rates of fibrosis progression. Based on previous studies, the correlation between ALDH2 and HCV could be explained by the two following aspects: enhanced virus replication and immunity suppression.

For one thing, the metabolite ACH could help to activate the expression of miR-122 and miR-34a, both able to stimulate HCV replication. Correspondingly, a large number of virus products brought about by strong virus replication will promote hepatocellular apoptosis. Apoptosis has a secondary amplification effect on the viral lethality in the liver, which not only delays virus clearance but also aggravates liver cell damage. And then, Kupffer cells and hepatic stellate cells (HSC) are driven by interleukins to aggregate and participate in the phagocytosis and clearance of apoptotic bodies. This process will accelerate the inflammatory responses and fibrogenesis in the liver. Meanwhile, ACH could increase the activity of protein phosphatase 2A (PP2A). PP2A could reduce methylation of signal transducer and activator of transcription (STAT)-1 and form the protein inhibitor of the activated STAT-1 PIAS-1-STAT-1 complex. Ultimately, the damage will enhance destruction of STAT-1 caused by HCV, thereby increasing the apoptosis (Fig. 3).

For another, some scientists have claimed that impairment of immunity is a probable cause. Ethanol exposure enhances the inhibitory effect of HCV on innate immunity, thereby activating the spread of the virus in the liver and eventually leading to impaired adaptive immunity. The expression of interferon-stimulated genes (commonly referred to as ISGs) compromises over 300 antiviral molecules that synergistically exert innate immunity and are under control of the catalysis of retinol and retinoic acid biogenesis. Interestingly, the toxicity of these two substances can be suppressed by ALDH metabolism. It means that inhibition of ALDH will hinder the body’s antiviral ability through the ISGs pathway. Therefore, one of the molecular mechanisms for the synergism between HCV and alcohol abuse in liver disease progression is hepatocyte metabolism involving ethanol-retinol metabolic competition.

In addition, activated T cells can be combined with other immune cells to form a positive feedback effect, being aroused by various cellular factors in turn, in a bid to stir up inflammation and inhibiting further liver damage. Gao et al. discovered the phenomena that alcohol-fed Aldh2−/− mice were less sensitive to concanavalin A-induced T cell hepatitis than wild type mice. Their further study suggested that ACH directly restrained cytokine production in T cells by means of the inhibition of aerobic glycolysis or stimulation of corticosterone release, leading to the occurrence of suppressed T cell hepatitis in ethanol-fed Aldh2−/− mice. What is more, there is a certain correlation between the HBV epi-
Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer mortality in the world. In China, HCC has emerged as one of the top three malignant tumors, according to rankings by prevalence and mortality. The prevalence rates of HCC were reportedly 0.03%, 0.01%, <0.01%, and <0.01% among the general population in China, the USA, Europe, and Japan, respectively. Meanwhile, HCC cases are increasing rapidly in China, which accounts for approximately 90% of all cases of primary liver cancer. Therefore, scientists have been endeavoring to explore the relationship between ALDH2 gene mutation and HCC (Table 2).

Generally, HBV infection and ALD are two major liver diseases with HCC developing tendency. Hou et al. inhibited aggressive behavior in vitro and in vivo by forcing the expression of ALDH2 in HCC cells. Recently, Liu et al. explored the association between ALDH2 polymorphisms and the risk of HCC among CHB patients, and their result showed that ALDH2 polymorphisms has nothing to do with HCC but does protect against developing HCC through habitual alcohol drinking, which was reported in another research study as well.

Similar, similarly, based on an analysis of 4,155 hepatitis B surface antigen seropositive participants, there is a distinct relationship between an increased risk of HCC in the HBV-positive cirrhosis population and ALDH2 gene polymorphisms. A meta-analysis conducted by Chen et al. found that the ALDH2 rs671 polymorphism is not associated with HCC susceptibility in East Asians, and this is similar to the conclusion from Liu et al. Interestingly, Huang et al. found that the ALDH2 polymorphisms had a certain impact on resolution of HCC in patients. The result showed that HCC patients with a defective allele of ALDH2 have a promising postoperative outcome, after Kaplan-Meier analysis and univariate followed by multivariate Cox proportional hazard analysis indicated that the GG genotype is an independent clinical predictor for shorter time-to-distant metastasis (adjusted p=0.019) and shorter overall survival (adjusted p=0.001). Although the ALDH2*2 mutation itself does not lead to liver cancer directly, it will reduce ALDH2 protein levels and liver enzyme, which eventually is related to the accumulation of ACH in the blood and carcinogenic mutations. Likely, the results of animal experiments show that the mouse ALDH2 (E487K) mutation significantly promotes the occurrence and development of mouse liver cancer.

Unfortunately, despite a series of strong evidence supporting ethanol as an environmental risk factor for HCC, the exact pathways by which alcohol causes HCC are still under exploration. ACH has been shown to affect DNA replication and repair mechanisms. After chronic alcohol exposure, Aldh2-deficient animals produce a large amount of harmful oxidized mitochondrial DNA via extracellular vesicles, which can be delivered into neighbor HCC cells and subsequently activate multiple oncogenic pathways, to promote HCC development (Fig. 4). What is more, consuming a large amount of ethanol induces microsomal ethanol metabolism by cytochrome P4502E1 (known as CYP2E1) and leads to additional production of acetaldehyde, as well as an in-
crease in free radicals that can result in cell death, DNA damage, and even production of other carcinogenic substances. Other hypothesized pathways have included the transactivator protein X that is encoded by HBV and remolded to the extracellular matrix through hypoxia-inducible factor-1α (HIF-1α) target genes and the lysyl oxidase (HIF-1α/LOX) pathway to promote HCC metastasis. The ALDH2-acetaldehyde-redox-AMP-activated protein kinase (AMPK) axis participates in the regulation of ACH levels, which is activated by ALDH2. Therefore, identifying ALDH2 expression levels in HCC might be a useful biomarker for determining prognosis and developing targeted therapies that are urgently needed to treat patients with HCC.

In addition, human liver cancer tissue test results show that ALDH2*2 protein is extremely unstable in human liver, and the low expression of ALDH2 protein has a certain correlation with the formation of liver cancer. The Journal of Hepatology also reports that a deficiency in the ALDH2 gene expression is associated with an increased risk of HCC in patients with hepatitis B cirrhosis who overtake alcohol. Both in vivo and in vitro studies have found that liver cells from ALDH2-deficient mice can produce a large amount of harmful oxidized mitochondrial DNA, which is transferred to adjacent liver cells through extracellular vesicles and can activate multiple carcinogenic pathways involving ACH (JNK, STAT3, BCL-2, and TAZ) to promote the occurrence of alcohol-related HCC.

**Table 2. Recent clinical studies on the relationship between the ALDH2 polymorphism and HCC**

| Author     | Year | Conclusion                                                                                       | Reference |
|------------|------|------------------------------------------------------------------------------------------------|-----------|
| Liu et al. | 2016 | Polymorphisms in ALDH2 had significant indirect effects on HCC risk, mediated through alcohol drinking. | 35        |
| Hou et al. | 2017 | Inhibiting aggressive behavior both in vitro and in mice by forcing the expression of ALDH2 in HCC cells. | 73        |
| Ye et al.  | 2018 | The mutant genotypes of ALDH2 may be protective factors for HCC susceptibility in Guangxi Province, China. | 74        |
| Chien et al. | 2016 | GG genotype of ALDH2 rs671 was an HCC risk predictor in cirrhotic chronic hepatitis B patients. | 75        |
| Seo et al. | 2019 | ALDH2 deficiency is associated with an increased risk of alcohol-related HCC development from fibrosis in human patients and in mice. | 76        |
| Chen et al. | 2020 | ALDH2 rs671 polymorphisms are not associated with HCC susceptibility in East Asians. | 77        |
| Huang et al. | 2019 | HCC patients carrying a defective allele of ALDH2 had a favorable postoperative outcome. | 78        |
| Jin et al. | 2015 | ALDH 2 plays a role of tumor suppressor by maintaining the stability of genome in the liver, and the common human ALDH 2 variant would become an important risk factor for hepatocarcinogenesis. | 79        |

**Abbreviations:** ALDH2, aldehyde dehydrogenase 2; CYP2E1, cytochrome P4502E1; HCC, hepatocellular carcinoma.

**Fig. 4. Effect of ALDH2 on HCC cells.** After chronic alcohol exposure, the Aldh2-deficient mice produce a large amount of harmful oxidized mitochondrial DNA which are delivered into neighboring hepatocellular carcinoma (HCC) cells via extracellular vesicles.
ALDH2 is a key enzyme in alcohol metabolism, and its genetic mutations are mainly clustered in East Asia. The genetic mutations of ALDH2 will depress ALDH2 enzyme activity and provoke accumulation of ACH, which will lead to the destruction of liver cells. Importantly, ALDH2 gene mutation and the potential impact of ACH on T cell response may become one of the factors affecting the progression of liver disease and outcomes of global liver disease. In conclusion, understanding the impact of disease progression related to the ALDH2 gene may be helpful for the improvement of future liver disease prevention strategies.

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**Conflict of interest**

The authors have no conflict of interests related to this publication.

**Author contributions**

Review design (BC), drafting of the manuscript and figure design (QW), language and grammar perfection (XL), revising the manuscript for important intellectual content (QW, BC, ZZ), critical revision (ZZ).

**References**

[1] Yoval-Sánchez B, Rodríguez-Zavaleta JS. Differences in susceptibility to inactivation of human aldehyde dehydrogenases by lipid peroxidation byproducts. Chem Res Toxicol 2012;25:722–729. doi:10.1021/tx200518u.

[2] Jackson B, Brocker C, Thompson DC, Black W, Vasiliou K, Nebert DW, et al. Update on the aldehyde dehydrogenase gene (ALDH) superfamily. Hum Genomics 2011;5:283–303. doi:10.1186/1479-7364-5-4-283.

[3] Vasiliou V, Pappa A, Petersen DK. Role of aldehyde dehydrogenase genes in environment and xenobiotic metabolism. Chem Biol Interact 2000;129:1–19. doi:10.1016/s0009-2797(00)00211-8.

[4] Fritz KS, Petersen DK. An overview of the chemistry and biology of reactive aldehydes. Free Radic Biol Med 2015;85–89. doi:10.1016/j.freeradicb.2012.06.025.

[5] Zambelli VO, Gross ER, Chen CH, Gutierrez VP, Cury Y, Mochly-Rosen D. Aldehyde dehydrogenase-2 reduces necroptosis in rodent models of acute inflammatory pain. Sci Trans Med 2014;6:251ra118. doi:10.1126/scitranslmed.3009539.

[6] Wang Q. et al: ALDH2 gene polymorphism and liver disease
Oniki K, Morita K, Watanabe T, Kajiwara A, Otake K, Nakagawa K, Chang Y, Cho YK, Kim Y, Sung E, Ahn J, Jung HS, Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of non-alcoholic fatty liver disease and nonalcoholic steatohepatitis: Implications of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84. doi:10.1002/hep.28431.

Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: A comprehensive review. World J Hepatol 2019;11:11–18. doi:10.4254/wjh.v11.i1.11.

Lee HW, Wong VW, Changing NAFLD epidemiology in China. Hepatology. 2019;70:1095–1098. doi:10.1002/hep.30848.

Hajfethalhal Khan, Torabi Sagivand B, McCullough AJ. Effect of alcohol consumption on survival in nonalcoholic fatty liver disease: A national prospective cohort study. Hepatology 2019;70:511–521. doi:10.1002/hep.30226.

Chang Y, Cho KY, Kim Y, Sung E, Ahn J, Jung HS, et al. Nonalcoholic fatty liver disease: A cohort study. Hepatology 2019;69:64–75. doi:10.1002/hep.29370.

Chen L, Lang AL, Pof D, Ding WX, Beier JJ. Vinyl chloride-induced interaction of nonalcoholic and toxicant-associated steatohepatitis: Protection by the ALDH2 activator Alda-1. Redox Biol 2019;24:101205. doi:10.1016/j.redox.2019.101205.

Oniki K, Morita K, Watanabe T, Kajiwara A, Otake K, Nakagawa K, et al. Long-term effect of the alcohol dehydrogenase 2 deficiency on non-alcoholic fatty liver disease. Nutr Diabetes 2016;6:e210. doi:10.1038/nd.2016.17.

Moaddab SY, Farajnia S, et al. Alcohol inhibits T-cell glucose metabolism and hepatitis in ALDH2-deficient mice and humans: roles of acetaldehyde and glucocorticoids. Gut 2019;68:1311–1322. doi:10.1136/gutjnl-2018-316211.

Guo R, Xu X, Babcock SA, Zhang Y, Ren J. Aldehyde dehydrogenase-2 plays a beneficial role in ameliorating chronic alcohol-induced hepatic steatosis and inflammation through regulation of autophagy. J Hepatol 2016;65:647–656. doi:10.1016/j.jhep.2014.10.009.

Ajamio MG, Rogers CM, Liang D, Le M, Mur M, et al. Role of SIRT1 in regulation of LPS- or two ethanol metabolites-induced TNF-alpha production in cultured macrophage cell lines. Am J Physiol Gastrointest Liver Physiol 2009;297:G147–G153. doi:10.1152/ajpgi.00016.2009.

Gao B, Tsukamoto H. Inflammation in alcoholic and nonalcoholic fatty liver disease: Friend or foe? Gastroenterology 2015;150:1704–1709. doi:10.1053/j.gastro.2015.06.033.

Ren T, Mackowiak B, Lin Y, Gao Y, Liu J, Gao B. Hepatic injury and inflammation alter ethanol metabolism and drinking behavior. Food Chem Toxicol 2016;90:272–279. doi:10.1016/j.fct.2016.02.011.

Zong W, Zhang W, Li Q, Xie G, Sun Q, Sun X, et al. Pharmacological activation of aldehyde dehydrogenase 2 by Alda-1 reverses alcohol-induced hepatic steatosis in mice. Proc Natl Acad Sci U S A 2014;111:5677–5682. doi:10.1073/pnas.1323017111.

Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. ALDH2 deficiency promotes ethanol-induced gut barrier dysfunction and fatty liver in mice. Alcohol Clin Exp Res 2015;39:1465–1475. doi:10.1111/ace.12777.

Zhu CP, Wang AQ, Zhang HH, Wan XS, Yang XB, Chen SG, et al. Research progress and prospects of markers for liver cancer stem cells. World J Gastroenterol 2015;21:12166–12172. doi:10.3748/wjg.v21.i42.12190.

Chaudhry KX, Sankar G, Shukla PK, Mir H, Gangwar R, Manda B, et al. ALDH2 deficiency promotes ethanol-induced gut barrier dysfunction and fatty liver in mice. Alcohol Clin Exp Res 2015;39:1465–1475. doi:10.1111/ace.12777.

Fredy F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. J Glob Oncol 2019;5:1–37. doi:10.3322/caac.21492.

Chaudhry KX, Sankar G, Shukla PK, Mir H, Gangwar R, Manda B, et al. ALDH2 deficiency promotes ethanol-induced gut barrier dysfunction and fatty liver in mice. Alcohol Clin Exp Res 2015;39:1465–1475. doi:10.1111/ace.12777.

Lee YG, Jeon TM. Modulation of the autophagy-lysosomal pathway in hepatocellular carcinoma using small molecules. Molecules 2020;25:1580. doi:10.3390/molecules25071580.

Heu G, Chen L, Liu G, Yang X, Zang J, Yan HK, et al. Aldehyde dehydrogenase-2 (ALDH2) opposes hepatocellular carcinoma progression by regulating AMP-activated protein kinase signaling in mice. Hepatology 2017;65:444–455. doi:10.1002/hep.29466.

Ye X, Wang X, Shang L, Zhu G, Su H, Han C, et al. Genetic variants of ALDH2-rs671 and CYP2E1-rs2031920 with hepatocellular carcinoma susceptibility in East Asians: a meta-analysis. J Hepatol 2016;65:1094–1103. doi:10.1016/j.jhep.2016.04.018.

Huang PH, Hu CC, Chen CH, Chen LW, Chien RN, Lin YS, et al. The protective allele of Aldehyde Dehydrogenase 2 gene is associated with favorable postoperative outcomes in patients with hepatocellular carcinoma. J Cancer 2019;10:5733–5743. doi:10.7150/jca.33221.

Jin S, Chen J, Chen L, Hsien G, Lin Z, Gross S, et al. ALDH2(E487K) mutation increases protein turnover and promotes murine hepatocarcinogenesis. Proc Natl Acad Sci U S A 2015;112:9088–9093. doi:10.1073/pnas.1507571112.

Ogawa T, Morishita T, Kanamori A, Okada T, Hidaka H, Dey A, et al. A novel P2Y2 receptor antagonist for the treatment of nonalcoholic fatty liver disease. Int J Mol Sci 2018;19:2258. doi:10.3390/ijms19082258.

Kolota A, Glibas D, Oczkowski M, Gromadzka-Ostrowska J. Oxidative stress parameters in the liver of growing male rats receiving various alco-
Wang Q. et al: ALDH2 gene polymorphism and liver disease

[82] Tse AP, Sze KM, Shea QT, Chiu ET, Tsang PH, Chiu DK, et al. Hepatitis trans-activator protein X promotes extracellular matrix modification through HIF/LOX pathway in liver cancer. Oncogenes 2018;7:44. doi:10.1038/s41389-018-0052-8.

[83] Cui YQ, Liu YJ, Zhang F. The suppressive effects of Britannin (Bri) on human liver cancer through inducing apoptosis and autophagy via AMPK activation regulated by ROS. Biochem Biophys Res Commun 2018;497:916–923. doi:10.1016/j.bbrc.2017.12.144.

[84] Gao Q, Zhu H, Dong L, Shi W, Chen R, Song Z, et al. Integrated proteogenomic characterization of HBV-related hepatocellular carcinoma. Cell 2019;179:1240. doi:10.1016/j.cell.2019.10.038.

[85] Zahid KR, Yao S, Khan ARR, Raza U, Gou D. mTOR/HDAC1 crosstalk mediated suppression of ADH1A and ALDH2 links alcohol metabolism to hepatocellular carcinoma onset and progression in silico. Front Oncol 2019;9:1000. doi:10.3389/fonc.2019.01000.