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Aldehyde Dehydrogenase 2 Deficiency and Associated Health Risks in East Asian Populations: An Overview

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KEYWORDS

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ABSTRACT:

When alcohol is consumed, *Alcohol dehydrogenase* metabolizes ethanol to a toxic metabolite called acetaldehyde. Mitochondrial *Aldehyde dehydrogenase 2* (ALDH2) is an enzyme produced by the liver that metabolizes acetaldehyde to a significantly less toxic acetate. Approximately, 30-40% of the Asian population have an inherited deficiency for *aldehyde dehydrogenase 2*, resulting in the accumulation of acetaldehyde. The facial flushing response secondary to alcohol consumption is a key biomarker for ALDH2 deficiency. This study focuses on the increased risk of esophageal cancer in East Asian populations with ALDH2 deficiency. In this review, 67 PubMed articles within the last 30 years were reviewed. Each article was based on studies that excluded animal preclinical work. Test subjects were limited to East Asian populations with and without the ALDH2*2 deficiency. Ethanol affects epigenetic methylation and acetylation patterns, which are important regulators of gene expression. Ethanol-induced hypomethylation can activate the expression of oncogenes which can result in malignant transformation. Clinicians can utilize patient data to customize treatment plans tailored to their patients who come from cultural backgrounds and have increased genetic and epigenetic risks. Recent studies have provided insight to what preventative strategies can be implemented to increase health outcomes and life expectancy in patients with ALDH2 deficiency. Further research should utilize prior risk assessment models to enhance ALDH2 screening techniques and ALDH2 deficient patient surveillance. There remain several gaps in research, including the role of ALDH in oncogenic signaling pathways and its use as a biomarker in cancer development or metastasis and surgical efficacy techniques in esophageal cancer treatment.

1. Introduction

Alcohol consumption has adverse effects on overall health, but a deficiency in a key enzyme in alcohol metabolite detoxification exacerbates this further. When alcohol is consumed, alcohol dehydrogenase metabolizes ethanol to a toxic metabolite acetaldehyde. Mitochondrial aldehyde dehydrogenase 2 (ALDH2) is an enzyme produced by the liver that metabolizes acetaldehyde to acetate. Approximately, 30-40% of the Asian population have an inherited deficiency for aldehyde dehydrogenase 2 [1]. More specifically, the variant form of the allele ALDH2*2 is most prevalent in Chinese-American, Han Chinese, Taiwanese, Japanese, and Korean populations [3]. People of Asian descent have lower rates of alcohol dependence compared to other ethnic groups. However, within the Asian population, relatively high rates of alcohol dependence exist among Koreans and Korean-Americans [4]. Social factors in reducing alcohol dependency in Asian populations may involve the numerous side effects of ALDH2 deficiency. Associated symptoms include but are not limited to facial flushing due to histamine release, nausea, and tachycardia. The facial flushing response secondary to alcohol consumption is a key biomarker for ALDH2 deficiency [5]. This may also influence the amount of alcohol consumed by Asian population in social settings. Clinicians and most of the public are educated on the general flushing response. However, this overview will focus on the clinical dangers and impending health risks associated with individuals who

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have inherited ALDH2 deficiency. Recent research has demonstrated ALDH2 deficiency is associated with multiple other disorders including cardiovascular disorders, oral cancer, gastrointestinal cancer, and behavioral deficits [9].

2. Genetics in ALDH2 Deficient Alcohol Metabolism

There are two variants of ALDH2 gene in East Asian populations that involve the replacement of glutamate (Glu) with Lysine (Lys) at codon position 487. The most studied single nucleotide polymorphism in the ALDH2 gene is rs671 resulting in this replacement [9]. A Glu allele encoding a protein with normal catalytic activity is documented as ALDH2*1. Alternatively, the inactive version of this protein is documented as ALDH2*2, see Figure 1 [5]. Lys/Lys homozygotes have no ALDH2 activity. Lys/Glu heterozygotes have significantly less than half of the ALDH2 activity of Glu/Glu homozygotes because the Lys allele acts in a semi-dominant manner. Reduction in ALDH2 activity seen in Lys/Glu heterozygotes is more than 100-fold [6]. ALDH2 Lys/Lys homozygotes have a significantly increased acetaldehyde concentration and experience higher symptomatic intensity. These individuals are unable to consume high amounts of alcohol compared to Lys/Glu heterozygotes who have less severe symptomatic effects [7]. This is significant in that Lys/Glu heterozygotes may consume higher amounts of alcohol and have increased acetaldehyde exposure over a long period of time. With societal and cultural influence and more acetaldehyde exposures, it is the low-activity ALDH2 Lys/Glu heterozygotes who are at a greater risk of developing cancer (ie: squamous cell carcinoma of esophagus) from long-term alcohol consumption [5].

3. Acetaldehyde Accumulation in ALDH2 Variants

Figure 1. The Ethanol Metabolic Pathway and the Role of the ALDH2 Variants in Acetaldehyde Accumulation [5].

Data from 10 Japanese studies showed that 41 to 51 percent of Japanese possessed at least one ALDH2*2 allele. This included 1 to 8 percent who were homozygous for ALDH2*2. Five studies of Korean and Korean-American samples showed 29 to 37 percent of Koreans had one ALDH2*2 allele. This included 2-3 percent who were homozygous for ALDH2*2. The ALDH2*2 allele was less common in aboriginal Chinese and Taiwanese samples. 2 to 12 percent of study participants were heterozygous and 0.3 percent were homozygous [3]. Among other Asian ethnicities, ALDH2*2 was less common. This included Filipinos, Indians, Malays, Siberian Yakuts, and Thais. Data from these studies indicated that under 10 percent of study participants had at least one ALDH2*2 allele [3]. It is illustrated through these studies that great diversity exists within various Asian ethnic groups in ALDH2*2 prevalence in both heterozygous and homozygous individuals. Further studies from Japanese samples with ALDH2 deficiency demonstrated reduced quantity and frequency of alcohol consumption. Studies show that by observation in general Asian populations, individuals who are alcoholics or who had alcoholic liver disease rarely had ALDH2 deficiency or an ALDH2*2 allele [6]. SJ Lewis performed a meta-analysis of studies focusing on the ALDH2 genotype and esophageal cancer. Lewis found that risk was reduced among ALDH2*2 homozygotes [odds radio (OR), 0.36; 95% confidence interval (95% CI), 0.16-0.80] and increased among heterozygotes (OR, 3.19; 95% CI, 1.86-5.47) relative to homozygotes [7]. This data provides strong evidence and confirms the claim that ALDH2*2 heterozygotes have a higher cancer risk as discussed previously. Lewis, et al. supports the idea that homozygote genotypes have a more intense adverse reaction to alcohol, thus lowering the total amount of alcohol consumed, and can be declared as protective compared to heterozygotes [7].

A cost-efficient screening strategy has been suggested involving a high-resolution melting analysis. This is considered a sensitive closed-tube method to determine single nucleotide polymorphisms focusing on ALDH2. This method takes approximately two hours and only costs 50 cents, suitable for population screening [9]. Another method includes polymerase chain reaction-based restriction fragment length polymorphism analysis that can distinguish two polymorphic alleles for ALDH2 that can be completed within 1.2 hours [9]. Another option involves a two-question screening tool predicting the ALDH2*2 variant with 90% sensitivity and 88%

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specificity in a population of Japanese males [20] as seen in Figure 2. This method involving questionnaire is suggested in locations with minimal genotyping resources [19]. Lastly, there is an ethanol patch test. Ethanol is applied to the skin, where it is metabolized to acetaldehyde. If this metabolite is not further metabolized to acetate, it causes vasodilation, which is detected visually as localized erythema [23]. However, the sensitivity and specificity for the ethanol patch test is much lower compared to the questionnaire. ER Gross and colleagues declare that the ethanol patch is less useful in screening for the ALDH2*2 variant [19].

2-Question Screening Tool for ALDH2 Deficiency

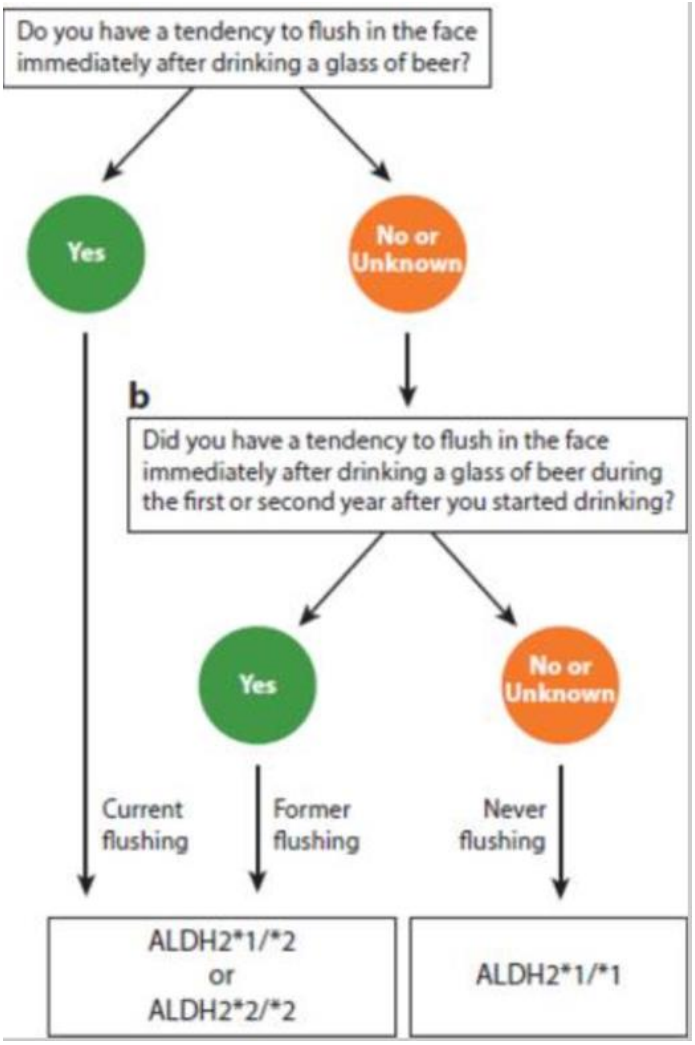

Figure 2. Questionnaire to predict ALDH2*2 genotype in Asian Americans. *A two-step questionnaire predicted with 90% sensitivity and 88% specificity in East Asian Japanese cancer-free men whether a person was either homozygous for ALDH2*1 or heterozygous or homozygous for ALDH2*2. Current flushing and former flushing are indicative of people who are either homozygous or heterozygous for the ALDH2*2 variant. [20]*

4. ALDH2 Deficiency and Cancer Risk

ALDH2 participates in the metabolism of ethanol and other cellular toxic aldehydes and oxidative stress-generated aldehydes that are associated with human diseases [19]. In 1988, the International Agency for Research on Cancer (IARC) considered the available evidence for the relationship between alcohol drinking and cancer risk of the liver and upper aerodigestive tract (UADT) including the oral cavity, pharynx, larynx and esophagus. Acetaldehyde is recognized by the IARC as

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a known Group I human carcinogen [21]. In 2007, Philip J. Brooks and colleagues formed a working group convened by the IARC. Based on evidence available from epidemiological and animal studies, Brooks and colleagues concluded that ethanol itself is carcinogenic to humans [2] rather than the ethanol metabolite acetaldehyde as stated by Yokohama, et al. Brooks argues that populations with fully active ALDH2, where acetaldehyde generated from ethanol oxidation is rapidly converted to acetate, different mechanisms of alcohol related UADT carcinogenesis are present, including the induction of CYP2E1 [2]. Genotoxic oxygen radicals and lipid peroxidation products are generated via CYP2E1 which are well documented to be present in the liver, however CYP2E1 is also present in esophageal cells where it is inducible by ethanol [2]. Brooks also states that another possibility involves a change in ethanol and acetaldehyde metabolism by microorganisms (bacteria and yeast) residing in the oral cavity. ALDH isozymes are differentially expressed in mucosal cells throughout the gastrointestinal tract. CP Chiang and colleagues studied the genetic association of allelic variations in gastrointestinal disorders focusing on functional expressions and cellular localization of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH). Genotypes of ADH and ALDH2 were determined by polymerase chain reaction-restriction fragment length polymorphisms. Gross ER and colleagues utilized the results to calculate ALDH2 activity in various human gastrointestinal tissues, represented in Table 1.

Table 1: ALDH2 activity reported in various human gastrointestinal tissues [a]

Tissue	ALDH2 activity (milliunit/g human tissue)	Calculated ADH:ALDH2*1/*1 activity ratio	Estimated ADH: ADH:ALDH2*1/*2 activity ratio	Estimated ADH:ALDH2*2/*2 activity ratio
Esophagus[b]	29.9	20.0	50.6	505.9
Stomach	132.0	1.8	4.5	45.1
Pancreas	213.0	0.3	0.8	7.5
Liver	1060.0	2.7	6.8	68.4
Colon	40.2	4.6	11.4	113.8
Rectum	41.8	7.3	18.2	182.4

[a] Table is based on values presented in Reference 22. AHD:ALDH2*1/*2 ratios were calculated assuming a 60% reduction in ALDH2 activity compared to ALDH2*1 and a 96% reduction in ALDH2*2/*2 activity.

Abbreviations: ADH, alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase 2 [22].

It is important to educate Asian-Americans of the increased risk factors associated with alcohol consumption, especially individuals with the ADHD2*2 variant. There are many social factors that may influence Asian Americans to continue participating in drinking socially such as college settings. O'Shea et al. examined the interplay between ALDH2*2 and peer drinking in college students by obtaining data from a freshman year university survey that included a saliva DNA sample [41]. In this study, Lys/Lys homozygotes and Lys/Glu heterozygotes were labeled as ALDH2*2(+) whereas normal Glu/Glu homozygotes were labeled as ALDH2*2 (-). Results showed greater alcohol consumption in individuals who ALDH2*2(-) and having more friends who also got drunk. The ALDH2*2 × peer drunkenness in individuals who ALDH2*2(-) and having more friends who also got drunk. The ALDH2*2 × peer drunkenness

[b]The lowest activity for ALDH2 and highest activity ratio for AHD:ALDH2 were found in the esophagus, suggesting acetaldehyde buildup in the digestive tract is highest in the esophagus [19, 22].

Interaction showed a stronger positive association with alcohol consumption for ALDH2*2(-) versus ALDH2*2(+) at increasing levels of peer drunkenness. Follow-up comparisons within each peer drunkenness

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level identified significantly higher alcohol consumption for ALDH2*2(-) compared to ALDH2*2(+) at the all friends got drunk level [41]. This displays how heterozygotes are likely to consume more alcohol compared to Lys/Lys homozygotes secondary to increased tolerance and decreased adverse effects.

5. Oral and Esophageal Cancers Secondary to Alcohol Consumption

Alcohol is an underestimated risk factor in the development of precancerous lesions in the oral cavity. 26.4% of all lip and oral cavity cancers worldwide are related to heavy alcohol consumption [8]. There are multiple lifestyle cofactors that contribute to the development of oral cancers such as alcohol consumption, cigarette smoking, poor oral hygiene, and genetic factors of alcohol metabolizing variants. These factors have been associated specifically with multiple squamous cell carcinoma in UADT tract [18]. Concentrations of acetaldehyde detected in the oral cavity are relatively high due to the metabolization of ethanol by oral microbes. The oral cavity, pharynx, larynx and esophagus are all locations highly susceptible to multiple primary cancers originated from squamous epithelia [17]. Acetaldehyde can directly damage the DNA by the formation of mutagenic DNA adducts and strand crosslinks. Studies have determined these changes to be GG to TT intrastrand mutations caused by acetaldehyde. This specific signature is called DBS2 in the COSMIC database [8]. Additionally, ethanol is known to affect epigenetic methylation and acetylation patterns, which are important regulators of gene expression. Ethanol-induced hypomethylation can activate the expression of oncogenes which can subsequently result in malignant transformation. The recent identification of ethanol-related mutational signatures emphasizes the role of acetaldehyde in alcohol associated carcinogenesis [8]. It is important to note the importance of screening and prevention regarding oral cancers due to the increased risk of developing second primary cancer. Mass screening data from Taiwan within 2004-2009 demonstrated that 158 out of 4,494 subjects with oral cancer developed second primary cancer of the hypopharynx and esophagus. The incidence rate was 6.47 per 1,000 person-years. Additionally, regression analyses showed the risk of a second primary cancer of the hypopharynx and esophagus was greater in alcohol drinkers than those who did not consume alcohol (aRR: 1.65, 95% CI: 1.20-2.48) [28].

Alcohol consumption is considered a risk factor for esophageal cancer associated with high levels of acetaldehyde exposure. Individuals with ALDH2 deficiency are at a greater risk for developing esophageal cancer than individuals who have normal ALDH2. Acetaldehyde is the most toxic ethanol metabolite in alcohol-associated carcinogenesis, while ethanol itself stimulates carcinogenesis by inhibiting DNA methylation and by interacting with retinoid metabolism [19]. The esophagus is exposed to many carcinogens, including alcohol and cigarette smoke. It remains unclear which alterations are the most critical for esophageal carcinogenesis [19]. Esophageal cancer is clinically seen as a male-dominant aggressive malignancy [25]. Histologically, esophageal cancer can be classified into esophageal squamous cell carcinoma (ESCC) or esophageal adenocarcinoma (EAC), where squamous cell carcinoma remains the most common globally [24, 25]. Eastern Asia has the highest population-attributable fraction of cancer caused by alcohol use, especially upper esophageal cancer, partly due to the high prevalence of the ALDH2*2 variant [27]. Rumgay et al. performed a population-based study to determine which demographics were affected the most using population attributable fractions (PAFs) calculated using a theoretical minimum-risk exposure of lifetime abstention and 2010 alcohol consumption estimates from the Global Information System on Alcohol and Health. Findings demonstrated that the highest PAFs of all new cases of cancer were observed in Eastern Asia and Central and Eastern Europe (5·7% [95% UI 3·6–7·9] and 5·6% [4·6–6·6], respectively. The lowest PAFs were in Northern African and Western Asian countries [27]. Lower expression of ALDH2 was consistently observed in tumor tissue samples compared to normal tissues that were tested not only for head/neck squamous cell carcinoma, but also for breast cancer, lung squamous cell carcinoma, and lung adenocarcinoma. Lower ALDH2 expression was also associated with poorer overall survival and poorer progression-free survival [29]. It is important to note that this study carried out by Chang and colleagues included individuals from mostly non-Asian descent.

Treatment includes endoscopic submucosal dissection (ESD) or minimally invasive esophagectomy (MIE).

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ESD is a complex operation and is associated with significant morbidity and mortality. MIE is becoming the standard of care and has a low mortality rate of 1.4% according to the University of Pittsburgh who performed MIE on 1011 patients [26]. In MIE, the esophagus is mobilized by video-assisted thoracoscopic surgery combined with laparotomy [30]. As surgeons worldwide began to adopt techniques to become competent in MIE, further research has enabled efficient ways to make MIE become the new standard for treatment. However, there are still complications associated with MIE including long total operative times, pulmonary infections, and cardiovascular complications including arrhythmia, heart failure, acute myocardial infarction, DVT, and PE. According to a study by SS Biere et al., the average operative time for minimally invasive esophagectomy via transthoracic approach transthoracic esophagectomy (MIE-TTE) was 329 minutes versus 299 minutes for open TTE (p=0.002) [31]. Although pulmonary infections were still associated with MIE, results from the same study with SS Biere revealed a significant decrease in pulmonary infection rates in MIE treated patients compared to the open esophagectomy group (29% versus 57%, p = 0.005) [31]. Yibulayin and colleagues demonstrated that MIE treated patients showed fewer cardiovascular complications (OR = 0.770, 95% CI = 0.681 – 0.872, $P_v < 0.05$), and surgical technology related complications (OR = 0.639, 95% CI – 0.522 – 0.781, $P_v < 0.05$), and lower in-hospital mortality (OR = 0.668, 95% CI = 0.539 – 0.827, $P_v < 0.05$) compared to patients who were treated via open esophagectomy [32]. In 2003, a robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) was developed to overcome the technical limitations of MIE [33]. Using this new technique, operative time reduced to an average range of 120-240 minutes and median blood loss was reduced to 400 ml [33] compared to 475 ml with open esophagectomy [32]. PC van der Sluis et al. performed a randomized controlled trial to evaluate the effectivity of RAMIE by assigning 112 patients with resectable intrathoracic esophageal cancer to either RAMIE or open transthoracic esophagectomy (OTE). Results showed that postoperative complications occurred less frequently after RAMIE (59%) compared to OTE (80%) [risk ratio with RAMIE (RR) 0.74; 95% CI, 0.57-0.96; P=0.02]. RAMIE resulted in less median blood loss (400 vs 568 mL, P <0.001), a lower percentage of pulmonary complications (RR 0.54; 95% CI, 0.34-0.85; P = 0.005) and cardiac complications (RR 0.47; 95% CI, 0.27-0.83; P = 0.006) and lower mean postoperative pain (visual analog scale, 1.86 vs 2.62; P < 0.001) compared to OTE. Functional recovery at postoperative day 14 was better in the RAMIE group [RR 1.48 (95% CI, 1.03-2.13; P = 0.038)] with better quality of life score at discharge [mean difference quality of life score 13.4 (2.0-24.7, p = 0.02)] and 6 weeks status post-discharge [mean difference 11.1 quality of life score (1.0-21.1; P = 0.03)] [34].

6. Acetaldehyde and Liver Disease

Alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH2) both have a key role in metabolizing ethanol consumed. These enzymes have highest concentrations in the liver but also present in many tissues. At high ethanol concentrations, oxidation of ethanol can become a major energy source and interferes with metabolism of other nutrients in the liver [6]. Pathophysiological effects may be mediated by the accumulation of acetaldehyde [6]. Individuals with ALDH2 deficiency who experience mild flushing and can tolerate heavy drinking may suffer from hepatic effects of elevated acetaldehyde concentrations. ALDH2*2 heterozygotes who drink alcohol heavily have been seen to develop alcoholic hepatitis at a lower cumulative alcohol consumption than those with active ALDH2 [6]. When the results of several studies were combined, the prevalence of ALDH2*2 was significantly higher in patients who were considered alcoholics and diagnosed with cirrhosis compared to patients without cirrhosis [6].

ALDH2 gene polymorphisms were studied and associated with increased rates of liver disease and cancer [9]. Prevalence rates for alcoholic liver disease are reported to be 4.5%, 6.2%, 6% and 1.56-2.34% in China, United States, Europe, and Japan respectively [10]. A meta-analysis including 12 studies showed that individuals with ALDH2*1 allele had a high frequency of alcoholic liver cirrhosis (ALC) compared to individuals with ALDH2*1/*2, or ALDH2*2 genotype [11]. In a study led by YC Chao, patients with alcoholic cirrhosis and alcoholic dependence had a significant lower frequency of the ALDH2*2 allele compared to the study's healthy controls (9%, 6% vs 30%, P<0.005; n=27, 50 and 50, respectively) [12]. Chao subsequently

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reported a significant higher frequency of the ALDH2*1 allele in patients with alcoholic cirrhosis compared to healthy controls (93% vs. 71%, P<0.001; 75 cases and 100 controls) [13]. To further support these findings, Lee et al. conducted a similar study including Korean individuals and reported a significantly higher frequency of the ALDH2*1 allele in patients diagnosed with alcoholic cirrhosis (96%, n=56) and in alcoholic individuals without evidence of liver disease (98%, n=52), in comparison with nondrinkers (74%, n=64, P=0.001) [14]. Interestingly, Edenberg et al. found that the frequency of ALDH2*2 allele increased in a group of alcoholic Japanese from individuals from 2.5% to 13% from 1979 to 1992 [9]. This is concerning regarding that ALDH2*2 allele's protective function may be associated with future increase in total alcohol consumption in heterozygotes, increasing tolerability to alcohol, and increase in alcohol related liver disease diagnoses. Individuals with ALDH2 rs671 polymorphism and other underlying conditions involving the liver must be aware of the increased dangers, risks and prognosis. MC Tsai et al. studied 1515 patients with cirrhosis, of which 342 were diagnosed with concomitant heavy alcoholism and HBV infection, 796 with HBV infection alone, and 377 with heavy alcoholism alone. In their 10-year cumulative incidences of HCC and mortality were significantly higher in patients with cirrhosis with HBV infection and alcoholism compared to those with HBV infection alone or alcoholism alone. Heavy alcohol intake and ALDH2 rs671 genotype were both associated with significantly increased risk of HCC and mortality in patient with HBV-related cirrhosis.

In 2015, liver cancer was ranked as the fifth most common cancer and second most malignant cancer for cancer-related mortality in the world [15]. ALDH allele has been studied and associated with hepatocellular carcinoma (HCC) risk, progression, and prognosis. A dose-dependent association between the cumulative amount of alcohol consumption over time and HCC risk in individuals with ALDH2*1/*1 or ALDH2*2/*2 genotype was reported based on a comparison of a cohort of 208 cases of patients diagnosed with HCC and a control cohort of 208 control patients in Jiangsu, China [15]. The results revealed that it was ALDH2 polymorphisms that had a significant interaction with heavy alcohol consumption in the development of HCC, suggesting that individuals with ALDH2*1/*2 or ALDH2*2/*2 genotypes are encouraged to reduce their consumption of alcoholic beverages to reduce risk of HCC. Decreased ALDH2 concentration levels may indicate poor prognosis in HCC patients, while forcing expression of ALDH2 in HCC cells inhibited cancer cell aggressive behavior in vitro and in mice by modulating the activity of ALDH2-acetaldehyde-redox-AMPK axis [16]. Guojun Hou et al. suggest that identifying ALDH2 expression levels in HCC might be a useful strategy for classifying HCC patients and developing potential therapeutic strategies targeting metastatic HCC [16].

ALDH2 is the key enzyme in acetaldehyde metabolism and therefore, an important therapeutic target for treatment. [9] It is known that acetaldehyde plays a role in liver inflammation, fibrosis, and cancer development. Further studies are needed to address the effects and particularity of ALDH2 polymorphisms in alcoholics to offer efficient dosages regarding ALDH2 altered functionality that may affect pharmacokinetics of substrate drugs and potential variable drug efficacy [9].

7. Cardiovascular Risks Associated with ALDH2 Deficiency

An increased incidence of myocardial infarction and coronary artery disease is strongly associated with ALDH2*2 variant individuals [19]. Takagi and colleagues performed a study that included 342 Japanese men with myocardial infarction (MI) and 1,820 cardiac disease-free men. Multiple logistic analyses indicated that the odds ratio of the Lys/Lys genotype compared to the Lys/Glu and Glu/Glu genotype was 1.56 (p=0.0359). Subjects with MI were noted to have higher body mass index, higher prevalence of Lys/Lys genotype, and lower high-density lipoprotein (HDL). Takagi concluded that the ALDH2 Lys/Lys genotype is a risk factor for myocardial infarction in Japanese males due to its influence on HDL cholesterol level [35]. A similar study was performed with Korean males by SA Jo and colleagues. In this study, 122 men, 60-81 years old, were randomly recruited from Yonsei University Medical Center. A total of 439 men ages 60-84 years, who did not have MI were selected as controls. Genotypes carrying the mutant ALDH2 allele (ALDH2*1/*2 plus ALDH2*2/*2) were significantly more frequent in patients with MI than in the controls (42.6% vs. 30.5%, P=0.0163). Multiple logistic regression analysis revealed that ALDH2*1/*2 plus ALDH2*2/*2, together with

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abnormal high density lipoprotein cholesterol and elevated body mass index, was an independent risk factor for MI in elderly Korean men (odds ratio=1.976, 95% CI: 1.202-3.248) [36]. Qi Wang et al. searched for a precise estimation of the relationship between the ALDH2 polymorphism and its influence on the susceptibility to CHD and MI by using nine case-control studies including a total of 7358 subjects. This group included 1961 CHD patients, 1040 MI patients, and 4257 healthy controls. Results from the meta-analysis showed that the ALDH2 rs671 polymorphism may be associated with increased risk of CHD (odds ratios [OR]=1.36, 95% confidence interval [CI]=1.06-1.75, p=0.017) and MI (OR=1.64, 95% CI=1.22-2.20, p=0.001) [37]. WK Cook et al. studied the relationship between alcohol consumption and cardiovascular disease while also focusing on ethnic prevalence of the variant ALDH2*2 stratified by gender. Alcohol consumption level was positively associated with hypertension in Asian males. Cook's study showed that consuming 7 to 14 drinks per week was associated with more than double the risk compared to individuals who were abstinent [40]. For females with ALDH2*2 variant, individuals who consumed more than 7 drinks per week had a higher risk of diabetes, hypertension, and cardiovascular disease [40]. The data demonstrates support in Cooks' conclusive statement that Asian Americans may have increased risk of cardiovascular disease-related conditions at relatively low alcohol consumption levels, especially in subjects with ALDH2*2 variant.

Additionally, there has been research focusing on increased stroke risk in patients carrying ALDH2*2 variant. Nagasawa et al. studied the association between a polymorphism of the ALDH2 gene and lacunar infarcts of the brain using a population-based, cross-sectional study on residents from two age groups including 61 and 72 year-olds [38]. In subjects with lacunar infarction, the genotype of ALDH2 *1/*1 was associated with a larger number of the lesion ['single' versus 'multiple' odds ratio (OR) 3.73, 95%CI: 1.43-9.74] in men [38]. The OR was comparable even after adjusting for alcohol consumption, tobacco habits, age, hypertension, hypercholesterolemia, and diabetes mellitus (DM) (OR 3.88; 95% CI: 1.10-13.66). In women, there was no significant association between the ALDH2 genotypes and lacunar infarcts. The present study revealed that the ALDH2 *1/*1 genotype was significantly associated with the prevalence of multiple lacunar infarcts in Japanese men [38]. An additional case study supported the preconceived notion that alcohol consumption increases risk of stroke. This case study involved two previously non-alcoholic healthy men who suffered from acute ischemic stroke after a single episode of binge drinking, see Figure 3 [39]. It is important to note that both men had a past medical history of hypertension and were also both heterozygous for ALDH2*2 [39]. The study was led by CL Lai who concluded that the risk of acute ischemic stroke in hypertension Asians with variant ALDH2*2 allele after binge drinking may increase cardiovascular stress due to prolonged elevation of blood ethanol and acetaldehyde levels [39].

Heavy alcohol drinking has been previously reported to be associated with hypertension. YS Park examined the association between changes in South Korean adults with facial flushing and hypertension across drinking behavior patterns. Park obtained data from the Korea Community Health Survey which was conducted in 2019. Data consisted of 118,129 participants, including 51,047 men and 67,082 women [48]. Participants were divided into five groups based on change in facial flushing (non-drinking, non-flushing to non-flushing, flushing to flushing, non-flushing to flushing, flushing to non-flushing). The risk of hypertension in each facial flushing group was analyzed by multiple logistic regression. Men in the non-flushing to flushing group had a significantly higher association with hypertension than other groups (men: odds ratio (OR) 1.42, confidence interval (CI) 1.14-1.76) [48]. According to the level of alcohol use disorder, the non-flushing to flushing group showed a significantly increased odds of hypertension compared to all levels of drinking (men: mild drinking: OR 1.95, CI 1.40-2.71; moderate drinking: OR 2.02, CI 1.41-2.90; women: moderate drinking: OR 1.71, CI 1.16-2.52; heavy drinking: OR 1.90, CI 1.19-3.04) [48]. This study found a significant association between changes in facial flushing and hypertension among adults in South Korea. In particular, individuals who changed from non-flushing to flushing reactions had an increased association with hypertension than the other groups. An additional study confirmed the prior observation that moderate and heavy alcohol consumption is associated with an increased risk of hypertension with individuals subject to facial flushing. MG Yoo performed a 12-year follow-up study analyzing 1,366 Korean participants

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who did not have hypertension at baseline [49]. Results indicated that in flushers, moderate and heavy alcohol consumption patterns increased the risk of incident hypertension compared with never-drinkers [moderate: HR 1.811 (95% CI 1.084-3.028); heavy: HR 2.494 (95% CI 1.185-5.247)], but non-flushers were not associated with increased risk of incident hypertension according to the alcohol consumption pattern [49]. In addition, a heavy alcohol consumption pattern increased the risk of hypertension among flushers compared with non-flushers [HR 2.232 (95% CI 1.054-4.728)] [49].

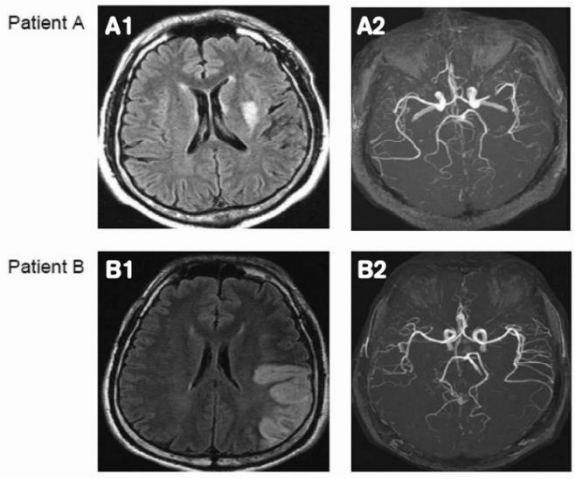

Figure 3. Brain images of two previously healthy men (Patients A and B) who developed acute ischemic stroke after a drinking binge.

A1: Axial FLAIR image showing a hyperintense lesion in the left basal ganglia.

A2: Brain MRA image showing a critical stenosis in the M2 segment of the left MCA.

B1: Axial FLAIR image showing a large hyperintense lesion in the left parietotemporal lobe.

B2: Brain MRA image showing normal intracranial vesicles [39].

The ALDH2 rs671 polymorphism is associated to increased risk of coronary artery disease [50]. H Han examined twelve case studies including 9616 patients who were included in a meta-analysis that showed patients possessing the rs671 polymorphism in the ALDH2 gene were associated with increased risk of CAD: (RR=1.20, 95%CI: 1.03-1.40, P=0.021) [50]. In a 2019 study led by S Zhong, ALDH2/LDLR double knockout mice had decreased atherosclerosis compared to LDLR-KO mice [51]. Additional findings demonstrated ALDH2/APOE-DKO (apolipoprotein E – double knockout) mice have increased atherosclerosis, suggesting an interaction of ALDH2 with LDLR [51]. AA Gibb evaluated this further and focused on how the ALDH2 SNP contributes to atherosclerosis based on Zhong's experiments. This revealed a pathway where the ALDH2 rs671 mutant is phosphorylated by AMPK, which is then translocated to the nucleus where it represses the transcription of lysosomal H+ pump subunit that is critical for lipid degradation and foam cell formation that occurs in atherosclerosis [52]. Gibb concluded that subjects carrying ALDH2 rs671 are at a greater risk for atherosclerosis and provide new targets for therapeutic intervention. Clinical studies have demonstrated a significant negative correlation between the severity of atherosclerotic plaque and activity of ALDH2 in patients with a medical history including coronary artery disease [53]. Interestingly, to support this claim, A Stachowicz et al. showed that Alda-1 (a specific agonist of ALDH2) can reduce the plaque area of ApoE$^{-/-}$ mice [54]. Focusing on inflammation, Zhang et al. discuss the role of NLRP3 (nucleus oligomerization domain like receptor family, pyrin domain containing 3) inflammasome and how activation of NLRP3 related pathways are closely related to the development and stability of plaques [55]. A previous study by C Pan showed that up-regulation of ALDH2 activity significantly reduced oxidative stress and the inflammatory response in human plaques [56]. With these findings, there is evidence that ALDH2 activation can simultaneously inhibit the priming and activation of NLRP3 inflammasome, inhibiting the development of atherosclerosis, and urging future research to determine if targeting NLRP3 inflammasome may be an efficient way of preventing atherosclerosis in patients.

8. Strategies to Counteract Facial Flushing

The visual symptoms of facial flushing can be a deterrent and worrisome sign for individuals who have the ALDH2*2 variant. However, this is not always true as studies show that facial flushing and other adverse effects are not certain to prevent risky alcohol consumption in college settings [43]. 336 Chinese-American and Korean-American students were classified as stable nonheavy drinkers, regressors, progressors, or stable heavy drinkers. Results indicated participants with

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ALDH2*2 alleles were more likely to be classified as stable nonheavy drinkers than as progressors (z = -2.49, p = .013). Higher levels of behavioral under control were associated with a greater probability of being classified as a stable heavy drinker relative to a stable nonheavy drinker (z = 2.26, p = .024). Stable heavy drinkers reported the most alcohol-related problems, whereas progressors reported more problems than either regressors or stable nonheavy drinkers, particularly at Year 2 [43]. Regarding the college setting, strong predictors of alcohol use represent different reasons for drinking which include tension reduction and enhancing sociability [44]. Students born in the United States consistently consume more alcoholic drinks, reach higher peak drinking levels, and drink more frequently than foreign-born students [46]. It is possible that lower rates of alcohol dependence among Asians are a result of strongly held cultural values that dictate drinking patterns that have evolved over centuries to minimize the negative effects of alcohol [47]. In another study focusing on mental health association with alcohol use, both anxiety and depression scores (high among college students) were both strongly associated with alcohol dependence symptoms [45]. This further provides reassurance that education on alcohol consumption should be brought to the forefront in a preventative effort regarding impending health risks to not only ALDH2*2 variant carrying subjects, but the public who may be susceptible to alcohol use.

There is significant research that explains that facial flushing is due to the inactive acetaldehyde dehydrogenase 2 enzyme that normally metabolizes acetaldehyde (metabolite from ethanol via alcohol dehydrogenase) to acetate. Research also indicates significant increased cancer risk associated with ALDH2*2 variant carrying individuals and elevated acetaldehyde levels in the blood. KG Chartier conducted a study to determine if college students understood this concept and how they are managing symptoms. The survey study included 335 White and Asian college students who reported facial flushing after consuming an alcoholic beverage [42]. Results demonstrated that 30% believed flushing had no meaning for drinking, 44.2% did not know what the symptom meant, 22.7% thought that flushing was a sign to stop drinking, and 3% thought that they could drink more [42]. Additionally, to manage facial flushing, 14.6% (n=47 students) have heard about taking over-the-counter medications to hide the flushing response, and 6% (n=20) students reported ever actually using over-the-counter medications (3.3% reported using heartburn medication, 1.5% allergy medication, 1,2% herbal or dietary supplement, and 0.9% other approach) [42]. Chartier notes that 14.04% of Asians in the study (n=16) used suppression strategies compared to 3.51% of Whites (n=4) [42]. This study clearly shows the importance of further education on this topic since the college students in this study were not well-aware of the meaning of flushing response. Further research is required to target efficient alcohol education in Asian college students who flush after drinking.

In a 2019 study by Y Matsumura, a one-time administration of an adeno-associated virus (AAV) gene transfer vector expressing the human ALDH2 coding sequence (AAVrh.10hALDH2) was performed to examine if this could correct the ALDH2 deficiency state [57]. This specific serotype was chosen because it predominantly targets the liver, the primary site of ethanol and acetaldehyde metabolism [58]. After this sequence was administered intravenously to ALDH2 knock-out ($Aldh2^{-/-}$) and ALHD2 E487K knock-in mice ($Aldh2^{E487+/+}$), acetaldehyde levels were measured after ethanol consumption [57]. Results indicated that untreated ALDH2-deficient mice had elevated acetaldehyde levels in contrast to treated $Aldh2^{-/-}$ and $Aldh2^{E487K+/+}$ mice who had lower serum acetaldehyde levels [57]. On top of increased ALDH2 activity, Alda-1 has been shown to inhibit alcohol-induced oxidative stress [60], and reduced esophageal DNA damage levels after ethanol consumption [61]. These findings bring interest to further in vivo trials to examine how AAV-mediated ALDH2 therapy may reverse the deficiency state in ALDH2*2 individuals to reduce facial flush and reduce the risk of associated disorders as discussed previously.

An alternative approach includes the use of nutrient supplementation to manage acetaldehyde levels. In a 2019 study, K Fujioka analyzed the effects of nutritional supplement Essential AD2 on individuals' acetaldehyde levels with ALDH2*2 mutant. Based on a 28-day open-label trial, 12 subjects genotyped to be heterozygous for the ALDH2 gene mutation participated in this study. ALDH2 deficient subjects showed a significant decrease in average blood acetaldehyde level 20 minutes after alcohol consumption (from 0.91 mg/dL to 0.71 mg/dL, P

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value = 0.02) after receiving 28 days of the nutritional supplement [59]. Acetaldehyde levels taken at 10 minutes and 40 minutes also showed a decrease, although they were not statistically significant [59]. In addition, safety tests looking at liver function tests showed a decrease in aspartate transaminase and alanine transaminase liver proteins from 27.3 to 15.2 and 20.9 to 13.2, respectively, over the 28 days [59]. This nutritional supplement shows benefit in reducing facial flushing and may display reduction in health risks associated with acetaldehyde levels.

SL McAllister discusses the importance of precision medicine when discussing the customized care to patients who are carrying the ALDH2*2 allele, originating from the East Asian descendants of the Han Chinese [62]. McAllister emphasizes the importance of considering lifestyle choices with patients in terms of risk for developing specific diseases, preventative screening, and selection of medications for treatment [62]. The efficacy of drugs is impacted by the ALDH2*2 variant [19]. For example, ALDH2 metabolizes nitroglycerin to nitric oxide which causes vasodilation. Individuals with ALDH2*2 variant are less efficient at metabolizing nitroglycerin to nitric oxide, resulting in decreased vasodilation. Data from a 2006 study led by Y Li demonstrated 10-fold decrease in catalytic activity to metabolize nitroglycerin for individuals with ALDH2*2 [63]. An additional study showed that by measuring forearm blood flow response to nitroglycerin in East Asian samples, ALDH2*2 variant subjects had a 40% reduced response in vasodilation compared to those without an ALDH2*2 variant [64]. There have also been studies that have shown decreased enzymatic activity in the commonly used antipyretic and analgesic, acetaminophen. YP Lee and colleagues found that acetaminophen (0.5 mM) decreased ALDH2 enzymatic activity in a dose-dependent manner from 0.2 to 1.0 mM (from 8.3% to 31%) [65]. This brings up concern when clinicians must reconsider recommending a very common over-the-counter medication to manage pain in patients with the ALDH2*2 variant. These studies bring light to precision medicine and high prevalence of the ALDH2*2 variant within the East Asian population. It is paramount for clinicians to consider if their patients who have this variant qualify for certain medications after considering the risks for specific diseases, such as limitations of drug metabolism. Z Lu found that ALDH2 activity was reduced in mice by 75% one hour after acetaminophen administration (350 mg/kd intraperitoneal) [66]. A decrease in ALDH2-mediated activity is not only seen in medications, but also in natural products. C Murata found that ALDH2 activity were affected by citral (found in lemon and lime), daidzin (found in kudzu, a Japanese arrowroot), areca nuts, and betel nuts [67].

9. Conclusion

ALDH2 plays a key role in the metabolism of ethanol after being consumed. In this overview, ALDH2 has been explored and strongly correlated to with progression to several adverse health disorders. There is a strong genetic component including the ALDH2*2 missense mutation when discussing the various diseases secondary to ALDH deficiency. On top of genetic risk factors, multiple behavioral factors play an integral part in the development of alcohol related liver disease, cancer, cardiovascular risks, and many subsequent diseases such as patients with head and neck cancer who may develop multiple cancers in the esophagus. In this case, ALDH2*2 patients who are susceptible to upper aero digestive tract cancers also manifest faster cancer progression and poor prognosis. Esophageal cancer continues to be a predominantly fatal disease with only mild improvements in survival rates over the past three decades. This brings attention to the importance of this research and clinical application to prevent such cases from progressing to a severe level. Clinicians may utilize this data to customize treatment plans tailored to their patients who come from specific cultural backgrounds and have increased genetic and epigenetic risks. ALDH2*2 is a widely studied variant allele in patients from East Asian backgrounds. Recent studies have provided insight to what preventative strategies can be implemented to increase health outcomes and life expectancy in patients with ALDH2 deficiency. Further research should utilize prior risk assessment models to enhance ALDH2 screening techniques and ALDH deficient patient surveillance. Clinicians should prioritize educating their patients while considering their genetics and treatment options, including precision medicine. There remain several gaps in research, including but not limited to the role of ALDH in oncogenic signaling pathways and its use as a biomarker in cancer development or metastasis, surgical efficacy techniques such as RAMIE versus open esophagectomy

in esophageal cancer treatment, and ALDH2*2 genotype as a risk factor for myocardial infarction, coronary artery disease, and stroke. Further research is necessary to obtain results and educate Asian Americans so they understand the risks of social behavior that can be observed in certain situations such as peer pressure in school, cultural factors, or work influence.

References

1. Seo W, Gao Y, He Y, Sun J, Xu H, Feng D, Park SH, Cho YE, Guillot A, Ren T, Wu R, Wang J, Kim SJ, Hwang S, Liangpunsakul S, Yang Y, Niu J, Gao B. ALDH2 deficiency promotes alcohol-associated liver cancer by activating oncogenic pathways via oxidized DNA-enriched extracellular vesicles. J Hepatol. 2019 Nov;71(5):1000-1011. doi: 10.1016/j.jhep.2019.06.018. Epub 2019 Jul 4. PMID: 31279903; PMCID: PMC6801025.
2. Brooks PJ, Goldman D, Li TK. Alleles of alcohol and acetaldehyde metabolism genes modulate susceptibility to oesophageal cancer from alcohol consumption. Hum Genomics. 2009 Jan;3(2):103-5. doi: 10.1186/1479-7364-3-2-103. PMID: 19164087; PMCID: PMC2814320.
3. Eng MY, Luczak SE, Wall TL. ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. Alcohol Res Health. 2007;30(1):22-7. PMID: 17718397; PMCID: PMC3860439.
4. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004 Aug;61(8):807-16. doi: 10.1001/archpsyc.61.8.807. PMID: 15289279.
5. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS Med. 2009 Mar 24;6(3):e50. doi: 10.1371/journal.pmed.1000050. PMID: 19320537; PMCID: PMC2659709.
6. Crabb DW, Matsumoto M, Chang D, You M. Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. Proc Nutr Soc. 2004 Feb;63(1):49-63. doi: 10.1079/pns2003327. PMID: 15099407.
7. Lewis SJ, Smith GD. Alcohol, ALDH2, and esophageal cancer: a meta-analysis which illustrates the potentials and limitations of a Mendelian randomization approach. Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1967-71. doi: 10.1158/1055-9965.EPI-05-0196. PMID: 16103445.
8. Hoes L, Dok R, Verstrepen KJ, Nuyts S. Ethanol-Induced Cell Damage Can Result in the Development of Oral Tumors. Cancers (Basel). 2021 Jul 30;13(15):3846. doi: 10.3390/cancers13153846. PMID: 34359747; PMCID: PMC8345464.
9. Wang W, Wang C, Xu H, Gao Y. Aldehyde Dehydrogenase, Liver Disease and Cancer. Int J Biol Sci. 2020 Jan 22;16(6):921-934. doi: 10.7150/ijbs.42300. PMID: 32140062; PMCID: PMC7053332.
10. Xiao J, Wang F, Wong NK, He J, Zhang R, Sun R, Xu Y, Liu Y, Li W, Koike K, He W, You H, Miao Y, Liu X, Meng M, Gao B, Wang H, Li C. Global liver disease burdens and research trends: Analysis from a Chinese perspective. J Hepatol. 2019 Jul;71(1):212-221. doi: 10.1016/j.jhep.2019.03.004. Epub 2019 Mar 12. PMID: 30871980.
11. He L, Deng T, Luo H. Aldehyde Dehydrogenase 2 (ALDH2) Polymorphism and the Risk of Alcoholic Liver Cirrhosis among East Asians: A Meta-Analysis. Yonsei Med J. 2016 Jul;57(4):879-84. doi: 10.3349/ymj.2016.57.4.879. PMID: 27189280; PMCID: PMC4951463.
12. Chao YC, Liou SR, Chung YY, Tang HS, Hsu CT, Li TK, Yin SJ. Polymorphism of alcohol and aldehyde dehydrogenase genes and alcoholic cirrhosis in Chinese patients. Hepatology. 1994 Feb;19(2):360-6. PMID: 7904979.
13. Chao YC, Young TH, Tang HS, Hsu CT. Alcoholism and alcoholic organ damage and genetic polymorphisms of alcohol metabolizing enzymes in Chinese patients. Hepatology. 1997 Jan;25(1):112-7. doi: 10.1002/hep.510250121. PMID: 8985275.
14. Lee HC, Lee HS, Jung SH, Yi SY, Jung HK, Yoon JH, Kim CY. Association between

polymorphisms of ethanol-metabolizing enzymes and susceptibility to alcoholic cirrhosis in a Korean male population. J Korean Med Sci. 2001 Dec;16(6):745-50. doi: 10.3346/jkms.2001.16.6.745. PMID: 11748356; PMCID: PMC3054808.

15. Global Burden of Disease Liver Cancer Collaboration; Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, Al-Raddadi R, Alvis-Guzman N, Amoako Y, Artaman A, Ayele TA, Barac A, Bensenor I, Berhane A, Bhutta Z, Castillo-Rivas J, Chitheer A, Choi JY, Cowie B, Dandona L, Dandona R, Dey S, Dicker D, Phuc H, Ekwueme DU, Zaki MS, Fischer F, Fürst T, Hancock J, Hay SI, Hotez P, Jee SH, Kasaeian A, Khader Y, Khang YH, Kumar A, Kutz M, Larson H, Lopez A, Lunevicius R, Malekzadeh R, McAlinden C, Meier T, Mendoza W, Mokdad A, Moradi-Lakeh M, Nagel G, Nguyen Q, Nguyen G, Ogbo F, Patton G, Pereira DM, Pourmalek F, Qorbani M, Radfar A, Roshandel G, Salomon JA, Sanabria J, Sartorius B, Satpathy M, Sawhney M, Sepanlou S, Shackelford K, Shore H, Sun J, Mengistu DT, Topór-Mądry R, Tran B, Ukwaja KN, Vlassov V, Vollset SE, Vos T, Wakayo T, Weiderpass E, Werdecker A, Yonemoto N, Younis M, Yu C, Zaidi Z, Zhu L, Murray CJL, Naghavi M, Fitzmaurice C. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol. 2017 Dec 1;3(12):1683-1691. doi: 10.1001/jamaoncol.2017.3055. PMID: 28983565; PMCID: PMC5824275.
16. Hou G, Chen L, Liu G, Li L, Yang Y, Yan HX, Zhang HL, Tang J, Yang YC, Lin X, Chen X, Luo GJ, Zhu Y, Tang S, Zhang J, Liu H, Gu Q, Zhao LH, Li Y, Liu L, Zhou W, Wang H. Aldehyde dehydrogenase-2 (ALDH2) opposes hepatocellular carcinoma progression by regulating AMP-activated protein kinase signaling in mice. Hepatology. 2017 May;65(5):1628-1644. doi: 10.1002/hep.29006. Epub 2017 Mar 31. PMID: 28027570.
17. Chen CH, Wang WL, Hsu MH, Mochly-Rosen D. Alcohol Consumption, *ALDH2* Polymorphism as Risk Factors for Upper Aerodigestive Tract Cancer Progression and Prognosis. Life (Basel). 2022 Feb 27;12(3):348. doi: 10.3390/life12030348. PMID: 35330099; PMCID: PMC8956056.
18. Toh Y, Oki E, Ohgaki K, Sakamoto Y, Ito S, Egashira A, Saeki H, Kakeji Y, Morita M, Sakaguchi Y, Okamura T, Maehara Y. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: molecular mechanisms of carcinogenesis. Int J Clin Oncol. 2010 Apr;15(2):135-44. doi: 10.1007/s10147-010-0057-6. Epub 2010 Mar 12. PMID: 20224883.
19. Gross ER, Zambelli VO, Small BA, Ferreira JC, Chen CH, Mochly-Rosen D. A personalized medicine approach for Asian Americans with the aldehyde dehydrogenase 2*2 variant. Annu Rev Pharmacol Toxicol. 2015;55:107-27. doi: 10.1146/annurev-pharmtox-010814-124915. Epub 2014 Sep 29. PMID: 25292432; PMCID: PMC4435945.
20. Yokoyama T, Yokoyama A, Kato H, Tsujinaka T, Muto M, Omori T, Haneda T, Kumagai Y, Igaki H, Yokoyama M, Watanabe H, Yoshimizu H. Alcohol flushing, alcohol and aldehyde dehydrogenase genotypes, and risk for esophageal squamous cell carcinoma in Japanese men. Cancer Epidemiol Biomarkers Prev. 2003 Nov;12(11 Pt 1):1227-33. PMID: 14652286.
21. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009 Nov;10(11):1033-4. doi: 10.1016/s1470-2045(09)70326-2. PMID: 19891056.
22. Chiang CP, Jao SW, Lee SP, Chen PC, Chung CC, Lee SL, Nieh S, Yin SJ. Expression pattern, ethanol-metabolizing activities, and cellular localization of alcohol and aldehyde dehydrogenases in human large bowel: association of the functional polymorphisms of ADH and ALDH genes with hemorrhoids and

colorectal cancer. Alcohol. 2012 Feb;46(1):37-49. doi: 10.1016/j.alcohol.2011.08.004. Epub 2011 Sep 22. PMID: 21940137.

23. Yokoyama A, Omori T. Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. Jpn J Clin Oncol. 2003 Mar;33(3):111-21. doi: 10.1093/jjco/hyg026. PMID: 12672787.
24. Rustgi AK, El-Serag HB. Esophageal carcinoma. N Engl J Med. 2014 Dec 25;371(26):2499-509. doi: 10.1056/NEJMra1314530. PMID: 25539106.
25. Abbas G, Krasna M. Overview of esophageal cancer. Ann Cardiothorac Surg. 2017 Mar;6(2):131-136. doi: 10.21037/acs.2017.03.03. PMID: 28447001; PMCID: PMC5387155.
26. Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M, Christie NA, Weksler B, Landreneau RJ, Abbas G, Schuchert MJ, Nason KS. Outcomes after minimally invasive esophagectomy: review of over 1000 patients. Ann Surg. 2012 Jul;256(1):95-103. doi: 10.1097/SLA.0b013e3182590603. PMID: 22668811; PMCID: PMC4103614.
27. Rumgay H, Shield K, Charvat H, Ferrari P, Sornpaisarn B, Obot I, Islami F, Lemmens VEPP, Rehm J, Soerjomataram I. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. Lancet Oncol. 2021 Aug;22(8):1071-1080. doi: 10.1016/S1470-2045(21)00279-5. PMID: 34270924; PMCID: PMC8324483.
28. Su WW, Chuang SL, Yen AM, Chen SL, Fann JC, Chiu SY, Chiu HM, Su CW, Hsu CY, Chen MK, Chen HH, Wang CP, Lee YC. Risk for a second primary hypopharyngeal and esophageal cancer after an initial primary oral cancer. Oral Dis. 2019 May;25(4):1067-1075. doi: 10.1111/odi.13080. Epub 2019 Mar 27. PMID: 30821883.
29. Chang PM, Chen CH, Yeh CC, Lu HJ, Liu TT, Chen MH, Liu CY, Wu ATH, Yang MH, Tai SK, Mochly-Rosen D, Huang CF. Transcriptome analysis and prognosis of ALDH isoforms in human cancer. Sci Rep. 2018 Feb 9;8(1):2713. doi: 10.1038/s41598-018-21123-4. PMID: 29426835; PMCID: PMC5807355.
30. Qureshi YA, Dawas KI, Mughal M, Mohammadi B. Minimally invasive and robotic esophagectomy: evolution and evidence. *J Surg Oncol*. 2016 Nov; 114(6):731–5.
31. Biere SS, Maas KW, Bonavina L, Garcia JR, van Berge Henegouwen MI, Rosman C, Sosef MN, de Lange ES, Bonjer HJ, Cuesta MA, van der Peet DL. Traditional invasive vs. minimally invasive esophagectomy: a multi-center, randomized trial (TIME-trial). BMC Surg. 2011 Jan 12;11:2. doi: 10.1186/1471-2482-11-2. PMID: 21226918; PMCID: PMC3031195.
32. Yibulayin W, Abulizi S, Lv H, Sun W. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. World J Surg Oncol. 2016 Dec 8;14(1):304. doi: 10.1186/s12957-016-1062-7. PMID: 27927246; PMCID: PMC5143462.
33. van Hillegersberg R, Boone J, Draaisma WA, Broeders IA, Giezeman MJ, Borel Rinkes IH. First experience with robot-assisted thoracoscopic esophagolymphadenectomy for esophageal cancer. Surg Endosc. 2006 Sep;20(9):1435-9. doi: 10.1007/s00464-005-0674-8. Epub 2006 May 15. PMID: 16703427.
34. van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, Kroese CC, Haj Mohammad N, Mook S, Vleggaar FP, Borel Rinkes IHM, Ruurda JP, van Hillegersberg R. Robot-assisted Minimally Invasive Thoracolaparoscopic Esophagectomy Versus Open Transthoracic Esophagectomy for Resectable Esophageal Cancer: A Randomized Controlled Trial. Ann Surg. 2019 Apr;269(4):621-630. doi: 10.1097/SLA.0000000000003031. PMID: 30308612.
35. Takagi S, Iwai N, Yamauchi R, Kojima S, Yasuno S, Baba T, Terashima M, Tsutsumi Y, Suzuki S, Morii I, Hanai S, Ono K, Baba S, Tomoike H, Kawamura A, Miyazaki S, Nonogi H, Goto Y. Aldehyde dehydrogenase 2 gene is a risk factor for myocardial infarction in Japanese men. Hypertens Res. 2002 Sep;25(5):677-81. doi: 10.1291/hypres.25.677. PMID: 12452318.
36. Jo SA, Kim EK, Park MH, Han C, Park HY, Jang Y, Song BJ, Jo I. A Glu487Lys polymorphism in the gene for mitochondrial aldehyde

dehydrogenase 2 is associated with myocardial infarction in elderly Korean men. Clin Chim Acta. 2007 Jul;382(1-2):43-7. doi: 10.1016/j.cca. 2007.03.016. Epub 2007 Mar 24. PMID: 17459359.

37. Wang Q, Zhou S, Wang L, Lei M, Wang Y, Miao C, Jin Y. ALDH2 rs671 Polymorphism and coronary heart disease risk among Asian populations: a meta-analysis and meta-regression. DNA Cell Biol. 2013 Jul;32(7):393-9. doi: 10.1089/dna.2013.1995. Epub 2013 May 22. PMID: 23697560.
38. Nagasawa H, Wada M, Arawaka S, Kawanami T, Kurita K, Daimon M, Adachi M, Hosoya T, Emi M, Muramatsu M, Kato T. A polymorphism of the aldehyde dehydrogenase 2 gene is a risk factor for multiple lacunar infarcts in Japanese men: the Takahata Study. Eur J Neurol. 2007 Apr;14(4):428-34. doi: 10.1111/j.1468-1331.2007.01700.x. PMID: 17388993.
39. Lai CL, Liu MT, Yin SJ, Lee JT, Lu CC, Peng GS. Heavy binge drinking may increase risk of stroke in nonalcoholic hypertensives carrying variant ALDH2*2 gene allele. Acta Neurol Taiwan. 2012 Mar;21(1):39-43. PMID: 22879089.
40. Cook WK, Tam CC, Luczak SE, Kerr WC, Mulia N, Lui C, Li L. Alcohol Consumption, Cardiovascular-Related Conditions, and ALDH2*2 Ethnic Group Prevalence in Asian Americans. Alcohol Clin Exp Res. 2021 Feb;45(2):418-428. doi: 10.1111/acer.14539. Epub 2021 Jan 22. PMID: 33349921; PMCID: PMC8545194.
41. O'Shea T, Thomas N, Webb BT, Dick DM, Kendler KS, Chartier KG. ALDH2*2 and peer drinking in East Asian college students. Am J Drug Alcohol Abuse. 2017 Nov;43(6):678-685. doi: 10.1080/00952990.2017.1314489. Epub 2017 May 4. PMID: 28471244; PMCID: PMC5916547.
42. Chartier KG, Tiarsmith EC, O'Shea T, Kendler KS, Dick DM. College students' use of strategies to hide facial flushing: A target for alcohol education. J Am Coll Health. 2020 Nov-Dec;68(8):922-926. doi: 10.1080/07448481. 2019.1640224. Epub 2019 Jul 30. PMID: 31361579; PMCID: PMC6989374.
43. Doran N, Myers MG, Luczak SE, Carr LG, Wall TL. Stability of heavy episodic drinking in Chinese- and Korean-American college students: effects of ALDH2 gene status and behavioral undercontrol. J Stud Alcohol Drugs. 2007 Nov;68(6):789-97. doi: 10.15288/jsad.2007.68. 789. PMID: 17960296.
44. Dick DM, Nasim A, Edwards AC, Salvatore JE, Cho SB, Adkins A, Meyers J, Yan J, Cooke M, Clifford J, Goyal N, Halberstadt L, Ailstock K, Neale Z, Opalesky J, Hancock L, Donovan KK, Sun C, Riley B, Kendler KS. Spit for Science: launching a longitudinal study of genetic and environmental influences on substance use and emotional health at a large US university. Front Genet. 2014 Mar 6; 5:47. doi: 10.3389/fgene. 2014.00047. PMID: 24639683; PMCID: PMC 3944794.
45. Armstrong TD, Costello EJ. Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. J Consult Clin Psychol. 2002 Dec;70(6):1224-39. doi: 10.1037//0022-006x.70.6.1224. PMID: 12472299.
46. Greene KM, Maggs JL. Longitudinal Change in Alcohol Use and Motivations for Drinking Among Asian American College Students. Alcohol Clin Exp Res. 2020 Oct;44(10):2109-2117. doi: 10.1111/acer.14436. Epub 2020 Oct 3. PMID: 33460235; PMCID: PMC7815956.
47. Newman I.M. Cultural aspects of drinking patterns and alcohol controls in China. The Globe (Institute of Alcohol Studies) 2002; 2002:18–21.
48. Park YS, Kang SH, Park EC, Jang SY. Association between changes in facial flushing and hypertension across drinking behavior patterns in South Korean adults. J Clin Hypertens (Greenwich). 2022 May;24(5):611-620. doi: 10.1111/jch.14475. Epub 2022 Apr 19. PMID: 35437944; PMCID: PMC9106078.
49. Yoo MG, Lee YJ, Jang HB, Kim HJ, Lee HJ, Park SI. Association between the incidence of hypertension and alcohol consumption pattern and the alcohol flushing response: A 12-year follow-up study. Alcohol. 2020 Dec; 89:43-48.

doi: 10.1016/j.alcohol.2020.07.001. Epub 2020 Jul 21. PMID: 32702501.

50. Han H, Wang H, Yin Z, Jiang H, Fang M, Han J. Association of genetic polymorphisms in ADH and ALDH2 with risk of coronary artery disease and myocardial infarction: a meta-analysis. Gene. 2013 Sep 10;526(2):134-41. doi: 10.1016/j.gene. 2013.05.002. Epub 2013 May 16. PMID: 23685282.
51. Zhong S, Li L, Zhang YL, Zhang L, Lu J, Guo S, Liang N, Ge J, Zhu M, Tao Y, Wu YC, Yin H. Acetaldehyde dehydrogenase 2 interactions with LDLR and AMPK regulate foam cell formation. J Clin Invest. 2019 Jan 2;129(1):252-267. doi: 10.1172/JCI122064. Epub 2018 Dec 3. PMID: 30375985; PMCID: PMC6307968.
52. Gibb AA, Elrod JW. Not just correlative: a new pathway defines how an ALDH2 SNP contributes to atherosclerosis. J Clin Invest. 2019 Jan 2;129(1):63-65. doi: 10.1172/JCI125433. Epub 2018 Dec 3. PMID: 30507608; PMCID: PMC6307930.
53. Lapenna D, Ciofani G, Ucchino S, Giamberardino MA, Di Ilio C, Cuccurullo F. Reactive aldehyde-scavenging enzyme activities in atherosclerotic plaques of cigarette smokers and nonsmokers. Atherosclerosis. 2015 Feb;238(2):190-4. doi: 10.1016/j.atherosclerosis.2014.11.028. Epub 2014 Dec 2. PMID: 25528427.
54. Stachowicz A, Olszanecki R, Suski M, Wiśniewska A, Totoń-Żurańska J, Madej J, Jawień J, Białas M, Okoń K, Gajda M, Głombik K, Basta-Kaim A, Korbut R. Mitochondrial aldehyde dehydrogenase activation by Alda-1 inhibits atherosclerosis and attenuates hepatic steatosis in apolipoprotein E-knockout mice. J Am Heart Assoc. 2014 Nov 12;3(6):e001329. doi: 10.1161/JAHA.114.001329. PMID: 25392542; PMCID: PMC4338726.
55. Zhang J, Liu X, Wan C, Liu Y, Wang Y, Meng C, Zhang Y, Jiang C. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1β production in inflammatory root resorption. J Clin Periodontol. 2020 Apr;47(4):451-460. doi: 10.1111/jcpe.13258. Epub 2020 Feb 7. PMID: 31976565.
56. Pan C, Xing JH, Zhang C, Zhang YM, Zhang LT, Wei SJ, Zhang MX, Wang XP, Yuan QH, Xue L, Wang JL, Cui ZQ, Zhang Y, Xu F, Chen YG. Aldehyde dehydrogenase 2 inhibits inflammatory response and regulates atherosclerotic plaque. Oncotarget. 2016 Jun 14;7(24):35562-35576. doi: 10.18632/oncotarget.9384. PMID: 27191745; PMCID: PMC5094945.
57. Matsumura Y, Stiles KM, Reid J, Frenk EZ, Cronin S, Pagovich OE, Crystal RG. Gene Therapy Correction of Aldehyde Dehydrogenase 2 Deficiency. Mol Ther Methods Clin Dev. 2019 Aug 26;15:72-82. doi: 10.1016/j.omtm.2019. 08.004. PMID: 31649957; PMCID: PMC68 04850.
58. Wang G, Qiu J, Wang R, Krause A, Boyer JL, Hackett NR, Crystal RG. Persistent expression of biologically active anti-HER2 antibody by AAVrh.10-mediated gene transfer. Cancer Gene Ther. 2010 Aug;17(8):559-70. doi: 10.1038/cgt. 2010.11. Epub 2010 May 7. PMID: 20448672; PMCID: PMC2906671.
59. Fujioka K, Gordon S. Effects of "Essential AD2" Supplement on Blood Acetaldehyde Levels in Individuals Who Have Aldehyde Dehydrogenase (ALDH2) Deficiency. Am J Ther. 2019 Sep/Oct;26(5):583-588. doi: 10.1097/MJT.0000 000000000744. PMID: 29509552.
60. Mitsuru Kimura, Akira Yokoyama, Susumu Higuchi. (2019) Aldehyde dehydrogenase-2 as a therapeutic target. *Expert Opinion on Therapeutic Targets* 23:11, pages 955-966.
61. Hirohashi K, Ohashi S, Amanuma Y, Nakai Y, Ida T, Baba K, Mitani Y, Mizumoto A, Yamamoto Y, Kikuchi O, Matsubara J, Yamada A, Miyamoto S, Seno H, Matsuda T, Muto M. Protective effects of Alda-1, an ALDH2 activator, on alcohol-derived DNA damage in the esophagus of human ALDH2*2 (Glu504Lys) knock-in mice. Carcinogenesis. 2020 Apr 22;41(2):194-202. doi: 10.1093/carcin/bgz091. PMID: 31074772; PMCID: PMC7175241.
62. McAllister SL, Sun K, Gross ER. Developing precision medicine for people of East Asian descent. J Biomed Sci. 2016 Nov 11;23(1):80. doi: 10.1186/s12929-016-0299-3. PMID: 27835996; PMCID: PMC5106841.

63. Li Y, Zhang D, Jin W, Shao C, Yan P, Xu C, Sheng H, Liu Y, Yu J, Xie Y, Zhao Y, Lu D, Nebert DW, Harrison DC, Huang W, Jin L. Mitochondrial aldehyde dehydrogenase-2 (ALDH2) Glu504Lys polymorphism contributes to the variation in efficacy of sublingual nitroglycerin. J Clin Invest. 2006 Feb;116(2):506-11. doi: 10.1172/JCI26564. Epub 2006 Jan 26. PMID: 16440063; PMCID: PMC1351000.
64. Mackenzie IS, Maki-Petaja KM, McEniery CM, Bao YP, Wallace SM, Cheriyan J, Monteith S, Brown MJ, Wilkinson IB. Aldehyde dehydrogenase 2 plays a role in the bioactivation of nitroglycerin in humans. Arterioscler Thromb Vasc Biol. 2005 Sep;25(9):1891-5. doi: 10.1161/01.ATV.0000179599.71086.89. Epub 2005 Jul 28. PMID: 16051882.
65. Lee YP, Liao JT, Cheng YW, Wu TL, Lee SL, Liu JK, Yin SJ. Inhibition of human alcohol and aldehyde dehydrogenases by acetaminophen: Assessment of the effects on first-pass metabolism of ethanol. Alcohol. 2013 Nov;47(7):559-65. doi: 10.1016/j.alcohol. 2013.09.001. Epub 2013 Oct 1. PMID: 24169088.
66. Lu Z, Bourdi M, Li JH, Aponte AM, Chen Y, Lombard DB, Gucek M, Pohl LR, Sack MN. SIRT3-dependent deacetylation exacerbates acetaminophen hepatotoxicity. EMBO Rep. 2011 Jul 1;12(8): 840-6. doi: 10.1038/embor.2011.121. PMID: 21720390; PMCID: PMC3147261.
67. Murata C, Suzuki Y, Muramatsu T, Taniyama M, Atsumi Y, Matsuoka K, Watanabe T, Okazaki I. Inactive aldehyde dehydrogenase 2 worsens glycemic control in patients with type 2 diabetes mellitus who drink low to moderate amounts of alcohol. Alcohol Clin Exp Res. 2000 Apr; 24(4 Suppl): 5S-11S. PMID: 10803771.