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Emerging Associations of the ALDH2*2 Polymorphism with Disease Susceptibility

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Abstract

Ethanol is metabolized by Alcohol Dehydrogenase (ADH) to acetaldehyde and then irreversibly oxidized by Aldehyde Dehydrogenase (ALDH) to nontoxic acetate. In individuals expressing the ALDH2*2 variant enzyme, the rate of conversion from acetaldehyde to acetate is reduced and leads to flushing, nausea, and tachycardia due to increased blood levels of acetaldehyde. The ALDH2*2 variant has a lowered NAD^+ coenzyme binding affinity, which results in a lowered clearance capacity toward acetaldehyde. This polymorphism is caused by the substitution of glutamate for lysine at position 487 within the catalytic active site of ALDH2, resulting in effects on subunit and quaternary complex activity. ALDH2*2 alleles are dominant over ALDH2*1 and therefore are expected to contribute to the formation of inactive heterotetramers decreased enzymatic activity in both homozygous and heterozygous individuals. Consequently, a higher susceptibility to various diseases such as Alzheimer's, osteoporosis, and acute coronary syndrome has been associated with ALDH2*2 carriers. Additionally, the polymorphism seems to affect the efficacy of Glyceryl Trinitrate (GTN), a drug intended to treat coronary heart disease, in carriers of ALDH2*2 alleles. However, the polymorphism is believed to afford a protective effect against alcoholism as the side effects of acetaldehyde build-up are undesirable. Disulfiram, a drug historically used to treat alcohol dependency, induces the same undesirable physiological effects as the variant enzyme in non-carriers by inhibiting the normal functioning of ALDH2 enzyme.

Keywords: Aldehyde dehydrogenase-2 (ALDH2); Polymorphism; Alcohol intoxication; Disulfuram; Nitroglycerin

Introduction

Approximately eight percent of the world's population inherits a point mutation in the Aldehyde Dehydrogenase-2 (ALDH2) gene. This polymorphism, referred to as ALDH2*2, is most prevalent in those of East Asian descent (Chinese, Japanese, Korean, and Taiwanese) and is rarely detected in non-Asian individuals. Because of this genetic variation, roughly 560 million people worldwide are particularly susceptible to alcohol intoxication [1-3]. The ALDH2*2 polymorphism encodes an inactivating, non-conservative amino acid substitution within the mitochondrial aldehyde dehydrogenase gene product [4]. An extensive body of literature has accumulated to describe the molecular underpinnings of the ALDH2*2 alcohol sensitivity phenotype and has revealed a compelling exemplar of an enzymatically dominant negative polymorphic gene product [4-10]. Recent data suggests, however, that sensitivity to alcohol intoxication may be only one of many susceptibilities of ALDH2*2 carriers. Here, we review the available published data concerning the role of ALDH2 in ethanol metabolism and associated phenotypic effects of ALDH2*2 polymorphism. We also point to a growing body of literature implicating ALDH2 in such diverse health effects as cancer, osteoporosis, and heart disease. Whether or not these additional disease phenotypes are dependent upon co-exposure to alcohol is yet to be firmly established. Figure 1 illustrates relative percentages of each disease linked to the ALDH2 polymorphism. Cumulatively, these recent findings highlight the need for reexamination of the role of ALDH2 in disease susceptibility and a reprioritization of research goals regarding the ALDH2*2 polymorphism.

Phenotypic variation in ethanol metabolism and ALDH2 polymorphism

Following alcohol consumption, ethanol is metabolized primarily in the liver. Here, Alcohol Dehydrogenase 1B (ADH1B) oxidizes ethanol to acetaldehyde. ADH is present in almost every bodily tissue and actively metabolizes numerous aldehydic compounds. After ADH1B converts ethanol to acetaldehyde, it is further oxidized by Aldehyde Dehydrogenase (ALDH) isoenzymes to nontoxic acetate using NAD^+ as a cofactor [11-17]. Two immunologically distinct ALDH isoenzymes have been identified: Cytosolic ALDH1 and mitochondrial ALDH2. Due to the lower Km value of ALDH2 for acetaldehyde in comparison to ALDH1, ALDH2 is considered to be the primary enzyme for ethanol metabolism in vivo. The ALDH2 gene is polymorphic with two allellic variations: The wild type ALDH2*1 allele and the alternate ALDH2*2 allele [18].

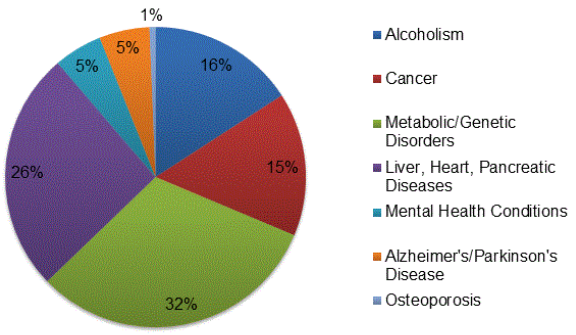

Figure 1: Relative percentages of "disorders" or "diseases" that have been associated with "ALDH2" polymorphism in the peer-reviewed scientific literature. The total number of papers published on the subject is ~46,000; however there is still disagreement on the mechanism of action and environmental factors influencing susceptibility and the onset of disease.

ALDH2*2 is an autosomal dominant allele; therefore, all carriers of even a single ALDH2*2 allele are physiologically affected by acetaldehyde toxicity following the consumption of ethanol [19,20]. Consequently, following ethanol exposure, ALDH2*2 carriers rely on less-active ALDH1 for acetaldehyde clearance and experience a flushing reaction to alcohol consumption due to elevated acetaldehyde in the bloodstream. This phenomenon has been firmly linked to the substitution of glutamate for lysine at position 487 within the catalytic active site of ALDH2, resulting in effects on subunit and quaternary complex activity. ALDH2*2 displays markedly reduced enzymatic activity toward acetaldehyde in comparison to ALDH2*1 [21]. Although the Km value for acetaldehyde is relatively unaffected by the Glu487Lys substitution (3.2 μM, versus 1 μM), the Km for NAD^+ (a necessary cofactor in acetaldehyde biotransformation) is markedly higher (70 μM for ALDH2*1 versus 7400 μM for ALDH2*2) [20-22]. Importantly, the Km for ALDH2*2 exceeds the available concentration of NAD^+ in the cell by about 15-fold [23,24].

Figure 2 depicts alcohol metabolism in a liver with homozygous expression of the ALDH2*1 enzymes (on the left) versus a liver with expression of ALDH2*2 enzymes (on the right). In both the ALDH2*2 and ALDH2*1 livers, ADH converts ethanol to acetaldehyde. In a liver with expression of the ALDH2*2 variant, the acetaldehyde substrate is not as effectively metabolized. Homozygous ALDH2*2/2 tetrameric gene products are expected to have less than 1-4% the activity of ALDH2*1/1 homotetramers, and the dominant negative effect of ALDH2*2 within the heterotetrameric complexes of heterozygotes results in less than 50% the activity of homozygous ALDH2*1 enzyme [12,21].

Characterization of ALDH2*2

ALDH2 was first identified in 1987, with the X-Ray crystallographic structure of the gene product elucidated in 1999 [25]. Although the ALDH2*1 allele is most common in populations worldwide, the allele frequency of the ALDH2*2 variation as either homozygous or heterozygous is 35-45% in East Asians [8,26]. All individuals with ALDH2 enzymatic deficiency examined to date remarkably carry the same amino acid substitution, which can be traced back approximately 2000-3000 years to the Han Chinese [27]. Luo et al. noted that the specific halpotype carrying the ALDH2*2 allele was highest in frequency in the Yunnan, South coastal, and East coastal areas of China and decreases in frequency further inland. According to archeological and historical evidence from this time period, evidence points to the Pai-Yuei tribe as an origin of the mutation, as they occupied the Southeastern coast of China into the Yunnan area as early as 16 B.C. The Pai-Yuei people established an independent country in this area, which lasted for around 160 years until it was conquered by other tribes. The Yuei people then scattered to other areas of South and Southwest China, Vietnam, and Thailand where they integrated with other tribes, especially the Han tribe [27]. This scattering correlates with the distribution of the ALDH2*2 mutation amongst people of East Asian descent.

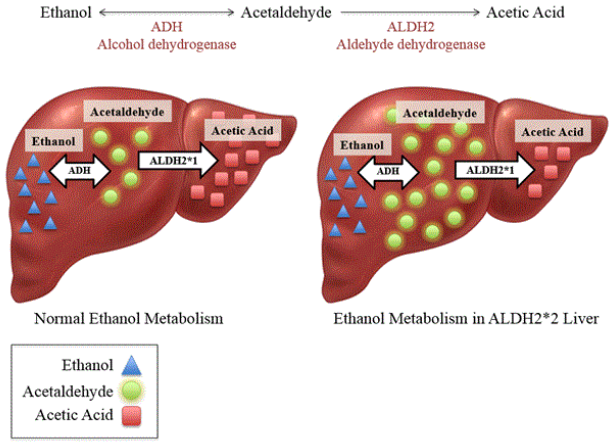

Figure 2: Normal ethanol metabolism versus metabolism in an ALDH2*2 liver (Figure modified from Chen et al., 1994).

The human ALDH2 gene is located on chromosome 12 and consists of 13 exons and 12 introns spanning approximately 44 kb [14,28,29]. The 517-amino acid gene product is expressed most abundantly in the liver and stomach, but is present in all tissues throughout the body [30]. The protein is posttranslationally processed and imported into the mitochondria of liver cells [22]. Protein translation begins in the cytosol, where a chaperone protein (hsp60 or hsp10) binds to the growing polypeptide chain to prevent folding [31]. After complete translation has occurred, a 17-amino acid transit sequence on the N-terminus of the polypeptide is recognized and transported to a receptor on the membrane of the mitochondria. Then, as the chaperone protein is removed, the polypeptide sequence is actively translocated through the inner and outer membrane of the mitochondria where the transit sequence is subsequently cleaved as part of the completion of folding and maturation of the enzyme inside the mitochondrial matrix [32]. In its mature form, the tetrameric enzyme is a homodimer of two dimers, where only two of the catalytic sites on the entire tetramer maintain activity. Each subunit contains three main domains: The catalytic domain, a NAD^+ binding domain, and an oligomerization domain [33].

In the enzymatic mechanism for ALDH-mediated oxidation, the first step involves NAD^+ binding at the active site followed by aldehyde binding [34]. Subsequently, a thiohemiacetal adduct is formed due to

the nucleophilic attack by cysteine 302 [35]. Wild-type ALDH2*1 has a compulsory ordered mechanism in which cysteine 302 acts as a nucleophile attacking the carbonyl group of the substrate aldehyde. Prior to the nucleophilic attack, glutamate 268 accepts a hydride from cysteine 302 rendering it a stronger nucleophile [1]. A hydride is then transferred from cysteine 302 to the NAD^+ cofactor and a high-energy thioester bond is formed between the aldehyde and the enzyme. Finally, the bond is hydrolyzed and NADH dissociates as a product; this is the rate-limiting step of acetaldehyde oxidation [1]. Because of the dramatic decrease in affinity of the ALDH2*2 enzyme for NADH, this mechanism cannot proceed at normal physiological concentrations of the cofactor.

Wild-type ALDH2*1 forms homotetramers in vitro. However, ALDH2*2 alleles are dominant over ALDH2*1 and therefore are expected to contribute to the formation of inactive heterotetramers (ALHD2*1/ALDH2*2) and decreased enzymatic activity in heterozygous individuals. Several hypotheses have been proposed to explain the inhibitory effect of ALDH2*2 subunits on tetramer enzymatic activity. Some have proposed that the two types of subunits (ALDH2*1/ALDH2*2) create an allosteric interaction within the heterotetramer, rendering the quaternary structure inactive. Others hypothesize that the ALDH2*2 subunits destabilize NAD^+ in the ALDH2*1 cofactor binding site [5]. Finally, additional data demonstrate a decrease in protein stability of the ALDH2*2 enzyme in comparison to ALDH2*1 [36].

ALDH2*2 and alcohol dependence

Alcoholism is considered a chronic condition in which an individual struggles to control alcohol intake. Numerous studies indicate that alcoholism is less prevalent in individuals who possess the ALDH2*2 allele, due to the undesirable effects of acetaldehyde buildup in the body [1,4]. Evidence of this phenomenon exists in a landmark study of 100 Chinese men by Thomasson et al. where there were striking differences between alcoholic and nonalcoholic participants in ALDH2 genotype and allele frequency. The ALDH2*2 allelic frequencies were significantly lower in nonalcoholic subjects than in alcoholic subjects (12% and 48% respectively) [4]. Furthermore, evidence is also found in a comparative study conducted by Hendershot et al that compares individuals with at least one ALDH2*2 allele to those with the ALDH2*1 homozygous genotype. Those with ALDH2*2 alleles self-reported significantly more negative evaluations of their own cognitive and behavioral impairment after consumption of alcohol [37]. The anticipation of overwhelmingly negative physiological reactions to alcohol may act as a deterrent to alcohol use in individuals who inherit the low-activity ALDH2*2 variant allele [4,37-39].

The dominant negative low enzyme activity associated with expression of the ALDH2*2 allele leads to undesirable physiological reactions that challenge a healthy liver following the consumption of alcohol [36]. In an ALDH2*1 homozygous individual, consumption of 0.5 g/kg of ethanol (equivalent to 3-4 drinks in an average weight male) led to a mean blood acetaldehyde concentration of 1.8 μM. In ALDH2*1/2 and ALDH2*2 individuals, the same dose of ethanol led to symptom-producing mean blood acetaldehyde concentrations of 57.5 and 108.7 μM respectively [22]. These data indicate that even those individuals heterozygous for ALDH2*1/2 are much more sensitive to alcohol intoxication than ALDH2*1 homozygotes [40].

Protection afforded by the ALDH2*2 allele against alcohol dependency is more closely associated with frequency of heavy drinking rather than the amount of alcohol consumed [18]. In a study of Asian-American college students, it was found that the ALDH2*2 allele reduced the frequency of binge drinking. Individuals who inherit the ALDH2*2 allele may adjust drinking habits in a way that alters the relationship between alcohol consumption and problems with dependence. These individuals may maintain similar drinking frequency to their peers (due to social pressures, etc.), however given their heightened physiological response to alcohol consumption, they may learn to regulate or pace their consumption to maintain lower levels of acetaldehyde blood concentration levels to avoid negative physiological consequences [18].

Several studies have suggested that the inheritance of the ALDH2*2 allele may also indirectly prevent severe and permanent liver damage from long-term alcohol abuse [41]. However, logically, individuals who do not consume alcohol are not at risk of developing alcoholic liver disease. By extension, individuals who express the ALDH2*2 enzyme and avoid heavy alcohol consumption have lower risk of alcohol related liver disease [42]. For example, the ALDH2*2 allele was found to be uncommon in Japanese patients with alcohol dependency syndrome and in those with liver disease, with a prevalence of only 2.3% in the alcohol dependent and 2.8% in non-dependent individuals with liver disease as compared to 41% in the general population of Japan [5].

Disulfiram and alcohol dependence

Disulfiram, commonly known by the trade name "Antabuse," has been used for over 60 years as a drug to treat alcoholism and underscores the fundamental role of ALDH2 in moderating risk of alcohol abuse [41]. The mechanism of action for disulfiram is to inhibit the normally functioning ALDH2 enzyme in order to give rise to negative physical responses such as nausea, vomiting, and hypotension when alcohol is consumed. The intent of disulfiram prescription is to mimic the ALDH2*2 low activity phenotype, causing a buildup of acetaldehyde in tissues. Hence, the goal in the development of disulfiram was to enable the ALDH2*1 population to experience the same protective effect against alcoholism.

In an examination of the possible in vitro mechanism of disulfiram, two methods were proposed. A study by Kitson et al. showed that disulfiram causes an initial partial inhibition of ALDH2 followed by a gradual and irreversible loss of enzymatic activity. Kitson proposed that disulfiram forms an intermolecular mixed disulfide with one of the active thiol sites on the enzyme, thereby reducing ALDH2*1 enzyme activity [41,43]. This mechanism is represented in Figure 3A. Conversely, Vallari and Pietruszko proposed a mechanism in which disulfiram binds to the active site thiol on one subunit and a cysteine residue on a neighboring subunit, possibly outside of the active site [11]. A potential intermediate in this mechanism would be an unstable intermolecular mixed disulfide, which would then stabilize the inactive form of the enzyme that contains two disulfide bonds to separate cysteine residues [11]. This mechanism is represented in Figure 3B. Both mechanisms involve the inactivation of the catalytic cysteine 302 residues by carbamylation in the substrate-binding site of the enzyme and the formation of an intermolecular dilsulfide bond [41]. This is similar to the binding of NAD^+ to the cysteine 302 residue in normal ALDH2 metabolism, except that in the case of disulfiram, the drug irreversibly binds to the same cysteine residue to prevent the binding of NAD^+. Studies have provided evidence to support Vallari in the hypothesis that disulfiram inhibits ALDH2 by forming an intramolecular dilsulfide bond involving cysteine(s) located at the

active site. However Kitson's proposition cannot be ruled out due to the rapidity of the conversion to an intramolecular disulfide bridge [41].

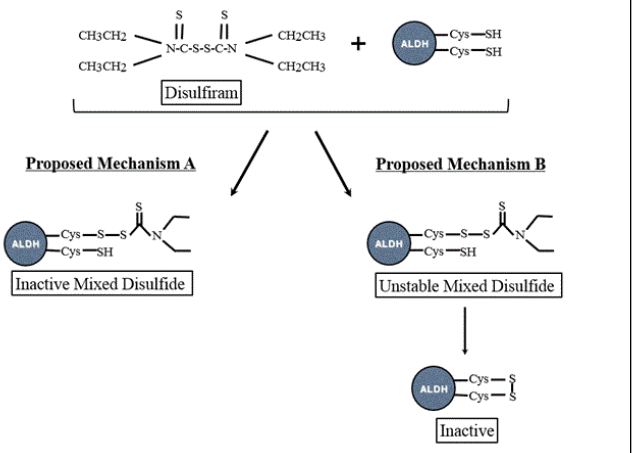

Figure 3: Proposed mechanisms of the disulfiram interaction with ALDH2.

Disulfiram has been approved by the United States Food and Drug Administration (US FDA) as an alcohol aversion therapeutic. However, alcoholism is still a major problem due to the poor compliance in drug usage that compromises the effectiveness of the treatment when prescribed. Other issues with disulfiram treatment include the progression of peripheral neuropathy [44,45]. This side effect is dose dependent and data suggest that the decreased ALDH2 activity and subsequent buildup of acetaldehyde is the cause of the disease, as in individuals possessing the ALDH2*2 mutation. A dose of greater than 250 mg/day is the greatest factor in causing symptoms, so reducing dosage or halting drug administration can reverse the symptoms in most cases [45]. Unfortunately for those who possess the ALDH2*2 mutation, no mechanism for restoring full enzymatic activity exists. Therefore, these individuals are more susceptible to developing alcohol induced peripheral neuropathy from the consumption of ethanol. In a study by Masaki et al., patients with the ALDH2*2 mutation had the highest incidence of peripheral neuropathy, while the lowest incidence occurred in those with the wildtype ALDH2, high activity phenotype [46].

Diseases associated with the inheritance of ALDH2*2

Numerous studies have concluded that there may be an association between the ALDH2 polymorphism and a wide range of health complications; Figure 1 describes disorders and diseases that have been associated with the ALDH2 polymorphism in a literature search. Although many of these associations exist, it does not necessarily causally link these diseases to a functioning or malfunctioning ALDH2 enzyme, as there could be multiple mechanisms and contributing factors leading to the development of these diseases and disorders. In the health complications discussed herein, multiple researchers believe through experimental evidence that these associations are linked the the ALDH2 polymorphism, however more studies need to be conducted to confirm these causally.

ALDH2*2 and disease among drinkers: In 2007, the International Agency for Research on Cancer (IARC) classified ethanol as a group 1 carcinogen in humans due to its metabolism to acetaldehyde its associated capacity to promote malignancy [47]. Since 2007, numerous epidemiological studies have investigated the link between inheritance of the ALDH2*2 allele and cancer susceptibility in the context of alcohol consumption. A 2015 meta-analysis of ALDH2*2 and all cancers, revealed roughly 20% increased cancer risk in ALDH2*2 homozygous individuals [48]. In site-specific studies, potential linkages of the ALDH*2 genotype to colorectal, stomach, pancreatic, breast, and head and neck cancers have been suggested. A subset of these site-specific cancers have been further investigated via meta-analyses [48-50]. Nonetheless, weak associations and study limitations prevent sweeping conclusions regarding the role(s) of ALDH2*2 inheritance in cancer risk. For example, in a meta-analysis of colorectal cancer (CRC) risk and the ALDH2 genotype, the ALDH2*2 allele was unexpectedly found to be protective of CRC [51]. The authors admit, however, that stratification according to drinking status was impossible due to inconsistencies in data collection among studies. More convincing data regarding ethanol consumption, ALDH2 genotype, and cancer risk has been documented in in vitro studies and mouse models [52-58].

ALDH2*2 and osteoporosis: Osteoporosis is characterized by a decrease in bone mineral density, bone mass, and bone strength, which ultimately leads to an increased risk of fracture [59]. In a genetic screen of known osteoporosis related genes in 403 elderly Japanese, ALDH2*2 was the only mutation strongly associated with the risk of osteoporosis [60]. This association was especially prevalent in ALDH2*2/2 homozygotes and in women. In support of this possible association between ALDH2*2 polymorphism and osteoporosis, evidence from rodent studies conducted at clinically relevant doses of acetaldehyde showed strong inhibitory effects toward formation of osteoblast progenitor cells [61]. In cultured mouse bone marrow cells incubated with 0.06% acetaldehyde (a similar concentration to that reached in vivo in humans with alcohol dependency), osteoblast formation was completely eliminated [1,61]. At a concentration of 0.004–0.02%, osteoblast formation was significantly decreased. Furthermore, in the same study, reduced osteoblast formation was also observed in human bone marrow cells derived from young adults with alcohol dependency. The confluence of osteoblast progenitors in this study was reduced to around 30% in cells derived from alcoholic dependent individuals as compared to age-matched samples from non-dependent individuals [61]. These data provide possible evidence for a direct relationship between acetaldehyde accumulation in the cells and osteoporosis, suggesting that ALHD2*2 may be a contributing factor to osteoporosis in East Asians who consume alcohol due to compromised clearance of acetaldehyde [62].

ALDH2*2 and heart disease: Acute Coronary Syndrome (ACS) is an umbrella term describing situations in which the blood supply to the heart is blocked. Acute coronary syndrome includes physiological conditions such as elevated blood pressure, heart attacks, and hypertension. Several studies have shown that the ALDH2*2 mutation is an independent risk factor for ACS [63-66]. More specifically, other studies have confirmed that an ALDH2 mutation is a strong risk factor for symptoms of elevated blood pressure and hypertension in males who consume high amounts of alcohol [67,68]. A recent study by Chang et al. supports these claims. Individuals who were homozygous for ALDH2*2/2 were more likely to be diagnosed with hypertension than those who did not carry the ALDH2*2 allele. Additionally, the risk for development of hypertension was higher in ALDH2*2 carriers who were heavy/moderate alcohol drinkers than those who did not drink alcohol, where the risk was completely absent [66]. From this, one can infer that individuals who inherit the ALDH2*2 allele have a

higher likelihood of developing symptoms of ACS from alcohol consumption, which puts a large percent of the Asian subpopulation at risk. The presence of an ALDH2*2 allele by itself is not causally associated with hypertension, rather consumption of alcohol in combination in individuals with the low activity variant which leads to an increase in acetaldehyde concentrations and in aids in the rapid diffusion of aldehydes across cellular membranes is causally associated with adverse physiological issues [1]. Those who express the wild type enzyme are less likely to develop disease from complications stemming from a decreased metabolic rate [28,42,48,50,51,69].

ALDH2*2 and disease unrelated to alcohol consumption: Ischemia occurs when blood flow to a certain tissue system is decreased, which can ultimately damage the tissue. In myocardial ischemia, most of the cardiac damage that occurs is believed to be due to excessive generation of reactive oxygen species, leading to peroxidation of unsaturated fatty acids that can form toxic end products such as the reactive aldehyde, 4-hydroxynonenal (4-HNE) [70,71]. Due to damage to the cardiac myocytes, excessive production of 4-HNE may ultimately impair cardiac contractility. ALDH2 has been shown to oxidize 4-HNE to a less reactive product and is hypothesized to be a protective factor [72]. Conversely, the ALDH2*2 genotype is thought to be associated with increased apoptosis and myocardial damage during ischemia [1,73]. In an in vitro study, in comparison to wildtype ALDH2*1, heterozygous ALDH2*2/1 tissues were highly sensitive to simulated ischemia in that they displayed significantly elevated levels of ROS and apoptosis [73]. Animal studies also support a role for ALDH2*1 in protection against myocardial ischemia. ALDH2*2 mice had exacerbated cardiac damage following ischemia-reperfusion as well as increased ROS production and endothelial dysfunction [74-76].

ALDH2*2 and Alzheimer's disease: Alzheimer's disease is characterized by progressive mental deterioration. Due to the nature and localization of the ALDH2 enzyme, certain studies have focused on understanding its role in Alzheimer's progression. In a study of more than 2,000 Japanese women, levels of serum lipid peroxidases, indicating the onset of Alzheimer's disease, were higher in ALDH2*2 carriers, even after an exclusion of drinking behaviors [77]. Other epidemiological studies indicate a possible higher incidence of Alzheimer's in people of Asian descent with the ALDH2*2 genotype [69]. In later stages of Alzheimer's neurodegeneration, there is a progressive loss in mitochondrial function and defects in mitochondrial metabolism develop. Inheritance of the ALHD2*2 allele has been linked to Alzheimer's due to a reduced ability to remove and detoxify the 4-HNE that accumulates in the hippocampal region of the brain [78]. Early stages of Alzheimer's disease generate reactive oxygen species, which result in the oxidation of lipid membranes and an accumulation of 4-HNE [79]. Researchers propose that the ALDH2*1 homozygous enzyme is effective at removing 4-HNE, while the presence a single ALDH2*2 allele is expected to impair this process, suggesting an association between an increased risk in developing Alzheimer's, oxidative stress, and ALDH2*2. This may also indicate that the removal of other toxic aldehydes could be inhibited by the ALDH2*2 mutation, but further study is needed. In an individual diagnosed with Alzheimer's, it is plausible that the disease may progress more rapidly in someone who possesses ALHD2*2 than someone who does not possess the mutation, although this is yet to be confirmed with reproducibility [76,80].

ALDH2*2 and drug use: Nitroglycerin, otherwise known as glyceryl trinitrate or GTN, was first developed and manufactured by Alfred Nobel in 1876 and has since been used to treat symptoms of coronary heart disease [81]. It is believed that GTN is biotransformed at least partially by mitochondrial ALDH2 to release pharmacologically active NO or S-nitrosothiol, which then activates cGMP-mediated cell signaling to relax vascular smooth muscle [33]. This drug has been extremely important in treating angina and heart failure for over 130 years and been called a "wonder drug" by patients who have used it correctly. However, in at least part of the Asian population this drug is has been proven to be ineffective (especially for those who inherit the ALDH2*2 mutation). The presence of the ALDH2*2 subunit limits GTN metabolic activation and therefore does not produce the intended effects against symptoms of coronary heart disease [33]. It was found that both homozygotes and heterozygotes have decreased efficacy of sublingual administration of GTN. The catalytic efficiency (Vmax/Km) of the ALDH2*2/2 enzyme was shown to be a mere 6-7% of that of the ALDH2*1/1 enzyme, while the ALDH2*2/1 enzyme showed intermediate efficiency (8-15% of the ALDH2*1/1 enzyme). Therefore, race may be an important factor in the utility and dose-response of this cardiovascular drug, and potentially other drugs affected by ALDH2.

Conclusion

The ALDH2 enzyme is one of the most important enzymes in converting ethanol to acetate in alcohol metabolism. Amongst the Asian population, it is fairly common to possess at least one polymorphic ALHD2*2 allele either in the homozygous or the heterozygous form, producing different levels of deficiency in the enzyme that ultimately translates into the mitochondria of the liver cells. The ALHD2*2 polymorphism in the second step of the oxidation reaction lacks an appropriate Km for the substrate NAD^+ as well as contains an altered substrate binding site and therefore has a lower affinity for acetaldehyde, causing a toxic buildup in the tissues. Acetaldehyde is considered a carcinogen and travels easily through cell membranes to other parts of the body which can cause many downstream problems. Complications can include head and neck cancers, esophageal cancers, heart complications, osteoporosis, Alzheimer's disease, and many others. However, it is important to note that due to the immediate negative physiological responses of an ALDH2*2 carrier after alcohol consumption, alcohol dependence and binge drinking activities are likely to decrease. This creates a protective affect by the ALDH2*2 enzyme. Similarly, the drug disulfiram inhibits normal ALDH2 activity, producing the same effect in wildtype homozygotes from alcohol that would be observed in ALDH2*2 carriers. Disulfiram is effective against alcoholism when taken by producing the same negative side effects as the ALDH2*2 polymorphism.

The ALDH2*2 polymorphism is well studied due to its major role in altering the effects of alcohol consumption in a large portion of the population. These studies have been important for not only those who possess the polymorphism, but also for the description of toxicity from ethanol metabolism byproducts for anyone who imbibes an ethanol-based product. Elucidating the mechanisms by which this specific polymorphism acts can aid future medical researchers in protecting those whose ALDH2 enzymes cannot properly process toxic aldehydes. Five hundred sixty million people currently carry this mutation and due to the genetic dominance of the ALDH2*2 allele, this number will likely grow in the future as it is passed onto heterozygous (ALDH2*1/2) children from carrying parents. Cumulatively, these studies suggest that new recommendations for the care of carriers of the ALDH2*2 allele should be considered.

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