HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 1 (2023)

The "Asian flush syndrome": ALDH2 Deficiency and Long-term Health Consequences

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ABSTRACT

Harmful use of alcohol leads to roughly 3 million deaths worldwide every year, and is linked to the development of roughly 230 different types of disease (*World Health Organization,* 2016). As alcohol has the ability to diffuse through cell membranes, its toxicity can heavily impact almost all organs within the human body. A large proportion of the East Asian population experiences the "Asian flush syndrome" post-drinking, which induces characteristic facial-flushing symptoms caused by an aldehyde dehydrogenase (ALDH2) enzyme deficiency due to an ALDH2 gene mutation. In the past, investigations on links between ALDH2 deficiencies and long-term health consequences have been conducted with conclusive evidence that confirm that "Asian flushers" have a predisposed risk for various diseases, including cancer and cardiovascular disease. This literature review systematically compiles research that explains the mechanisms behind ALDH2 deficient communities and increased health risks to esophageal cancer, cardiovascular disease, and Alzhiemer's disease. Furthermore, it shows that risk levels for disease are compounded when alcohol intake is increased. The preventative measures and social factors are also considered, including recommendations for further interventions to increase awareness and decrease alcohol intake in affected individuals.

Introduction

Alcohol-flush reaction and ALDH2 deficiency

The alcohol-flush reaction, "Asian flush" or "Asian glow," is a characteristic physical reaction involving the reddening of the face and neck following alcohol consumption found in roughly 40% of Eastern Asian populations (Brooks et al., 2009). Alcohol-flush reaction is one of the myriad of alcohol-induced symptoms including nausea, headache, hypotension, and tachycardia that may be caused by a genetic deficiency of the ALDH2 gene, depending on level of enzymatic activity (Brooks et al., 2009). As ALDH2 codes for the corresponding enzyme that is crucial in metabolizing acetaldehyde to acetate, a deficiency in enzymatic activity leads to the rapid accumulation of toxic acetaldehyde which directly induces facial flushing and other symptoms mentioned above (Brooks et al., 2009). There are two main ALDH2 alleles detected in these populations, differing by the placement of a normal activity glutamate (Glu) allele with an inactive lysine (Lys) allele at residue 487 (Brooks et al., 2009). The Glu allele is referred to as ALDH2*1, while the Lys allele is referred to as ALDH2*2 (Brooks et al., 2009). The Lys/Lys homozygous variant (ALDH2*2/*2) have no detectable ALDH2 activity, the Lys/Glus heterozygotes (ALDH2*1/*2) have less than 10 percent ALDH2 activity, and the fully-active wild-type Glus/Glus homozygote (ALDH2*1/*1) has 100 percent ALDH2 activity (Crabb et al., 1989). As a result, ALDH2*2/*2 homozygotes have 18 times higher and ALDH2*1/*2 heterozygotes have 5 times higher peak blood alcohol levels than normal function ALDH2*1/*1 homozygotes when the same volumes of alcohol are consumed (Lewis et al., 2005). Levels of ALDH2 activity are inversely related to severity of alcohol-induced physical symptoms; the lower the activity level, the more symptoms are present, and the higher the severity. Therefore, ALDH2*2/*2 homozygotes may actually face lower rates of long-term risk factors than other

genotypes, as the intensity of alcohol-induced symptoms refrains them from over-drinking, which in turn prevents rising levels of acetaldehyde (Brooks et al., 2009). As ALDH2*1/*2 heterozygotes still have present yet low levels of enzymatic function, symptoms are less severe, disposing individuals to over-drink and risk long term damage from acetaldehyde accumulation (Brooks et al., 2009).

Overview of risk factors

Excess acetaldehyde not only manifests in negative short-term physical symptoms of alcohol intoxication, but is also a known mutagen and animal carcinogen proven to cause DNA damage and have other cancer-promoting effects (Brooks et al., 2009). The ALDH2*2 allele have been observed to be at higher risk for developing esophageal cancers in studied Eastern Asian populations, especially China, where annual death rates surpass 200 thousand (Yang et al., 2020). Various studies have also linked ALDH2 polymorphisms with increased risk for cardiovascular disease and associated factors contributing to risk, mediated by alcohol consumption (Wang et al., 2020). Finally, ALDH2 polymorphisms are linked to increased levels of mitochondria dysfunction, a known cause of Alzhimer's disease (Kamino et al., 2000).

Methodology

Data collection

As more patterns in health risks are being observed in ALDH2-deficient individuals, recent literature has been concerned with investigating links between ALDH2 mutations and related risks. This review aims to systematically compile available literature and summarize the most common long-term health-related impacts inactive/low-functioning ALDH2 has on affected individuals.

Research publications and academic search engines that were consulted in this process include Pubmed, ScienceDirect, and Google Scholar. Advanced searches were performed with these keywords: "ALDH2" and "esophageal cancer" OR "cardiovascular disease" OR "Alzhiemer's disease." Certain variations and abbreviations were also used in place of keywords, such as replacing "aldehyde dehydrogenase 2" for "ALDH2" and "AD" for "Alzhiemer's disease." Searches were conducted in English only. In total, roughly 5600 articles were retrieved. 80 articles were selected for title relevance and were then organized in a spreadsheet for further inspection. The abstracts were read, and 41 were excluded for irrelevance. Furthermore, 6 articles were excluded for the inability to access the full text. The entirety of the article was then read, and 18 were excluded for similar data. Fifteen articles included in this literature review. Additionally, sources were consulted for the discussion section of this review in order to address ALDH2 deficiency-associated disease prevention and East Asian drinking patterns. For this portion of the study, four sources were found through searches involving keywords "ALDH2," "prevention," and "social impacts," OR "ALDH2" and "drinking patterns." Figure 3 is a diagram of the combined methodology used.

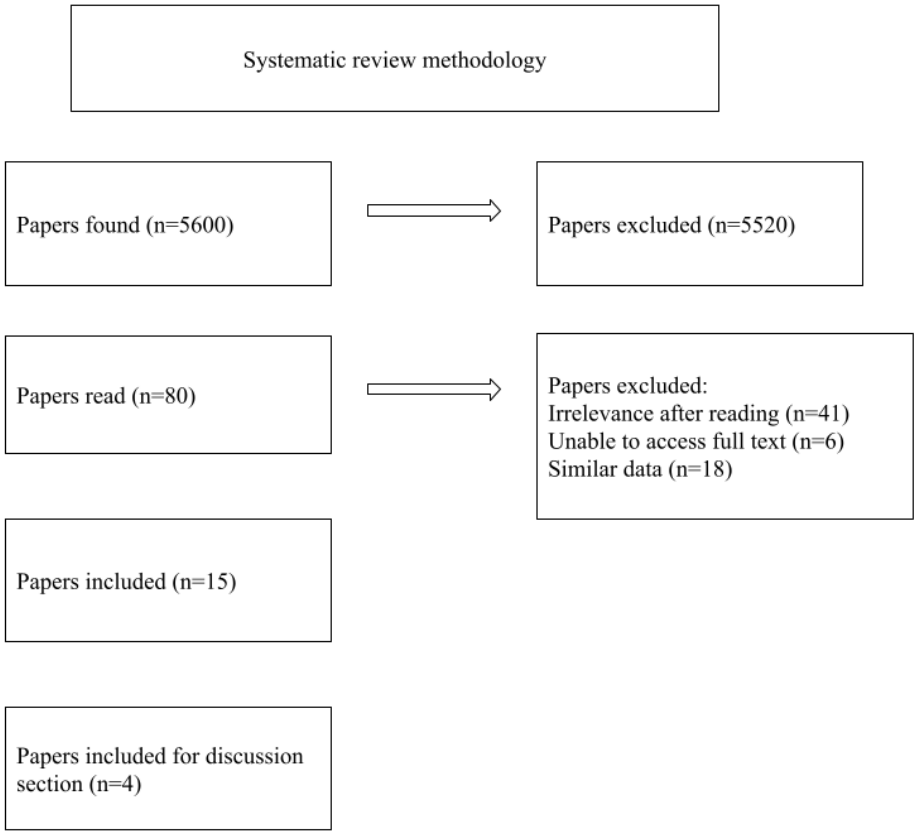

Figure 1: Chart of systematic review methodology used, including the total number of papers found, read, excluded, and included.

Common methods of ALDH2 diagnostic testing

Because alcohol-flushing (and the accompaniment of its associated symptoms) immediately following alcohol consumption is almost always a direct indication of a ALDH2 deficiency, clinical diagnoses can generally be made accurately without any other tests (Brooks et al., 2009). For instance, a two-question Japanese questionnaire with an 89% mean sensitivity value and an 89.5% mean positive predictive value was created to correctly identify individuals with deficiencies (Brooks et al., 2009). The questions included are as follows: (A) Do you have a tendency to develop facial flushing immediately after a glass (about 180 ml) of beer?; (B) Did you have a tendency to develop facial flushing immediately after a glass of beer in the first one or two years after you started drinking? For each question, the choices of “yes”, “no”, or “unknown” were given (Brooks et al., 2009). As ALDH2 enzymes are also present in human skin, ethanol patch tests can also be used to determine ALDH2 enzymatic activity ethanol (Hu et al., 2022). Typically, 0.1 ml of 70% ethanol is placed on a lint patch fixed on adhesive tape and placed on the upper arm for 7 minutes (Brooks et al., 2009). A skin patch with erythema after a time period of 10-15 minutes after removal is judged as positive (Brooks et al., 2009). The mean positive predictive value for this test was measured to be as high as 90% (Brooks et al., 2009). Some reviewed studies additionally tested for specific ALDH2 genotypes using polymerase chain reaction (PCR) tests, although this is generally not needed for an ALDH2 deficiency diagnosis (Crabb et al., 1989).

Results

Increased risk for esophageal cancer

ALDH2 deficiency increases risk for developing esophageal cancers as acetaldehyde is able to induce DNA-damage when not metabolized into acetate, causing DNA adducts, single- and/or double-strand breaks (DSB), point mutations, sister chromatid exchanges (SCEs), and DNA-DNA cross-links (Mizumoto et al., 2017). Following this discovery, the International Agency of Research on Cancer categorized acetaldehyde from alcohol-consumption as a "group 1 carcinogen" for the esophagus and/head and neck regions (Mizumoto et al., 2017). In Eastern Asian populations, esophageal squamous cell carcinomas (ESCCs) are most common out of all esophageal cancers, with ALDH2*1/*2 heterozygotes at the highest risk (Yokoyama et al., 2001). A meta-analysis found that individuals with ALDH2*1/*2 had a 7.12-fold increased risk of developing an ESCC when compared to individuals with fully active ALDH2*1/*1 homozygote (Mizutoto et al., 2017). Furthermore, this risk is compounded to a 13.5-fold increase when ALDH2*1/*2 individuals are alcoholics–defined when individuals meet or exceed the DSM-IV-TR Diagnostic Criteria for Alcohol Abuse and Dependence (Mizumoto et al., 2017). Similar levels of risks are confirmed in other studies. Case studies in Japan and Taiwan have stated significant causal relationships between alcohol consumption in low-functioning ALDH2*1/*2 heterozygotes and ESCCs, with measured odds ratios ranging from 3.7 to 18.1 in groups categorized by alcohol consumption level (Brooks et al., 2009). In these studies, a proportion as high as 58% to 69% of esophageal cancer risk was linked to alcohol consumption with low-function ALDH2*1/*2 genotypes (Brooks et al., 2009). Interestingly, in one study conducted in Japanese, Taiwanese, and Thai populations, ALDH2*2/*2 homozygotes gave an overall odds ratio of 0.36–a *reduced* risk for developing esophageal cancer when compared to the active function ALDH2*1/*1 homozygotes, as alcohol consumption is lower within ALDH2*2/*2 homozygous groups (Lewis et al., 2005).

Increased risk for cardiovascular disease

Similar to ALDH2 polymorphisms and its relationship with esophageal cancer, an increased risk for cardiovascular disease is generally associated with high levels of alcohol consumption in ALDH2 deficient populations rather than the deficiency itself. Several studies have examined this hypothesis. One analysis in Asian-Americans belonging to groups of either high prevalence of ALDH2*2 alleles or low prevalence ALDH2*2 alleles evaluated these factors with alcohol-consumption levels, instances of cardiovascular disease, and associated risk factors, such as hypertension, diabetes, and high cholesterol (Cook et al., 2021). This study found that in general, males of any ALDH2*2 levels who were moderate drinkers (more than 7 but less than 14 drinks per week) were marginally associated with higher levels of risks for hypertension and cardiovascular diseases (both $p<0.1$) when compared to populations that did not have the ALDH2*2 allele but consumed the same level of alcohol per week (Cook et al., 2021). Another study on ALDH2 polymorphisms in Chinese populations and incidence of major cardiovascular risk factors conversely found that higher incidences of hypertension, diabetes, and obesity were more significantly associated with populations *without* ALDH2*2 than with ALDH2*2 (all $p<0.01$) (Wang et al., 2020). In males only, incidences of ALDH2*1/*2 heterozygotes and ALDH2*2/*2 homozygotes has decreased with the increase of multiple cardiovascular risk factors when compared to the ALDH2*1/*1 wild-type (Wang et al., 2020). Furthermore, females who had more than 7 drinks per week with high prevalence for ALDH2*2 alleles were marginally associated with increased diabetes risks ($p<0.1$) when compared with populations with low prevalence for ALDH2*2 alleles, although ALDH2*2 high-prevalence females who had 7 or less drinks per week were marginally associated with lower cholesterol levels ($p<0.1$) than ALDH2*2 low-prevalence levels (Cook et al., 2021). Despite all this, there are still higher risk of complications independent of alcohol-consumption associated with ALDH2*2 in individuals who have already been diagnosed with cardiovascular diseases, namely coronary artery disease (CAD) (Zhang et al., 2015). In one such study, ALDH2*2

genotypes were statistically correlated with female patients who had type II diabetes mellitus (T2DM) (p=0.011), a condition also occurring in roughly half of all coronary artery disease patients (Xu et al., 2009). Logistic regression analysis showed that after being adjusted for factors including alcohol consumption, this value remained similar (Xu et al., 2009).

Links to Alzheimer's disease

Inactive ALDH2 genotypes can cause mitochondrial dysfunction from amyloid beta accumulation–a hallmark of Alzhiemer's disease. (AD) (Desler et al., 2018). Although evidence directly connecting the ALDH2*2 allele and Alzhiemer's is not abundant, several risk factors such as increases in mitochondrial reactive oxygen species (ROS) and changes in essential cellular bioenergetics have been recorded, which can significantly increase risk for AD (Desler et al., 2018). One study found that in both control and Alzhiemer's patients with ALDH2 polymorphisms, overexpression of ALDH2*2 led to a substantial increase in mitochondrial ROS and reduced ATP pools in fibroblasts, which was further exacerbated when ethanol exposure was introduced (Joshi et al., 2019). In Japanese populations, possession of ALDH2*2 allele results in an overall increase in late-onset AD risk (OD=1.6) (Kamino et al.,), while similar results but higher ratios were found in Chinese populations (OD=3.11). (Wanng et al., 2007) However, other studies did not find such results. Because the risks and underlying mechanisms of AD are not yet well known, more research will be necessary to determine the connections between ALDH2*2 and AD incidence and progression.

Risks in non-drinkers

For the most part, there are no associated risk factors related to ALDH2 deficient individuals who are non-drinkers, as the aforementioned risk factors are amplified not simply from ALDH2 mutated polymorphisms but its combination with alcohol consumption. For instance, a meta-analysis showed that there were no significant increase in risks of esophageal cancer in ALDH2 heterozygotes than ALDH2*1/*1 homozygotes. (OR=1.31) (Lewis et al., 2005). Furthermore, esophageal cancer has less of a correlation with low-activity ALDH2 genotypes in rural China (OR=1.7), where drinking levels are lower, than in Japan and Taiwan (ORs=3.1) (Brooks et al., 2009). Lowering alcohol consumption in a dose-dependent manner has been found to lower blood pressure, which greatly reduces risk for cardiovascular disease. (Wang et al., 2020). Finally, astrocytic-induced neuroinflammation, which is seen in many Alzhiemer's patients with overexpression of the ALDH2*2 allele, was greatly reduced with ethanol reduction and aldehydic load, suggesting strong links between alcohol consumption and Alzhiemer's risk factors (Joshi et al., 2019).

Discussion and Conclusion

Significance of risk factors

From these results, links between ALDH2*2 genotypes and ESCCs, cardiovascular diseases and risk factors including CAD and T2DM, and AD are confirmed to exist. However, this evidence also suggests that damage to long-term health is mediated by alcohol-consumption, as ALDH2 deficient non-drinkers do not face significant risk when compared to active ALDH2 individuals. Results showed an increased risk for ESCCs in ALDH2*1/*2 heterozygotes when compared to the wild-type control group, and an even higher risk when the recorded ALDH2*1/*2 groups consisted of alcoholics. This was expected, as although ALDH2*1/*2 heterozygotes experience alcohol-flushing reactions following drinking, symptom intensity is lesser than those of ALDH2*2/*2 homozygotes, resulting in larger amounts of alcohol consumption and higher levels of acetaldehyde accumulation and long-term health risk. At the same time, ALDH2*2/*2 homozygotes actually had a reduced risk for ESCCs when compared to the wild-type control group. As

ALDH2*2/*2 homozygotes incidences among heavy drinkers and alcoholics were the lowest out of all ALDH2 genotypes, this could be attributed to lower overall levels of drinking (lower levels of acetaldehyde) and thus lower levels of ESCC risk in these individuals.

Similar results were obtained from cardiovascular disease and AD results. Results in relation to cardiovascular disease risks showed links between increased levels of ALDH2 alcoholism and increased incidences of hypertension and cardiovascular disease in males. However, cardiovascular risk factors were more associated with individuals that do not possess the ALDH2*2 allele than those who do. This could be explained by the fact that levels of drinking are higher in populations without ALDH2*2 than with those who do, which is also evident in alcohol's role in long-term health consequences of ALDH2 deficient individuals. Results also showed existing evidence of a link between ALDH2*2 and T2DM, a risk factor for CAD, independent of alcohol consumption. However, the mechanisms behind this are not well known and require further study.

In the ALDH2 and AD studies, results showed increases of ALDH2 alcoholism with factors contributing to mitochondrial dysfunction, including increases of ROS and changes in cellular bioenergetics. Furthermore, dysfunction was exacerbated with alcohol consumption. Links between late-onset AD and ALDH2 were also found.

Although more research is necessary to understand the underlying mechanisms that determine ALDH2 deficiency and health consequences as well as specific risk factors in different demographics, results collected in this review collectively point to the conclusion that alcohol consumption coupled with ALDH2 deficiencies are able to increase risk for long-term damage and degenerative disease due to rapid levels of acetaldehyde accumulation.

Prevention and public awareness

As previously established, damage from acetaldehyde is mediated primarily by alcohol consumption, and risk factors for developing esophageal cancer, cardiovascular disease, and AD are all increased in groups with overall higher alcohol intake levels, regardless of ALDH2 genotype. Therefore, lowering the risk factors heightened in ALDH2 inactive populations will involve the root of the problem–lowering alcohol intake itself.

Though drinking levels in Asia are generally lower than most of Europe and North America, differences in consumption can vary between countries. Furthermore, social factors unique to East Asian environments can pressure individuals into drinking, and thus increase levels of negative health effects in ALDH2-deficient communities (Çakar et al., 2015). For instance, South Korea's workplace drinking culture has contributed to making the nation the highest hard liquor consumer, at 11.2 shots per week (Çaker et al., 2015). In a survey, 47.1% of all respondents said that they drink regularly to socialize with co-workers and colleagues. Furthermore, it is reported that 87% of South Korean employees drink at least once per week, and 23% binge drink (defined by drinking five or more shots in one go) at least once weekly (Çaker et al., 2015). In Japan, *Ikkinomi,* which involves gulping liquor in one shot and is a welcoming tradition in colleges and businesses, has led to acute alcohol intoxication–in 1996, 9971 people in the Tokyo metropolitan area were taken to the hospital due to acute alcohol intoxication (Peele et al., 1999).

In many ALDH2-deficient populations in East Asia, there is a lack of awareness of the health consequences that are associated with Asian flush syndrome and alcohol-consumption. In a survey done in Singapore focus groups, those who experienced flushing reactions to alcohol did not consider themselves as having increased risks of experiencing short- and long-term effects from alcohol consumption, compared to non-flushing groups (Kim et al., 2019). Additionally, 58% of the entire sample group did not believe that any connections existed between alcohol-flushing and long-term health consequences (Kim et al., 2019). This is evident that more awareness surrounding drinking levels and ALDH2-deficient individuals is necessary to lower risk factors for these communities.

Future interventions in the community

Much more research and public health work has been done on developing unique strategies to alleviate the long-term health consequences of ALDH2 deficiencies-related drinking, which involve tackling the social aspects that contribute to drinking culture and a lack of knowledge in East Asian communities. It is proposed that government incentives and educational programs on risk factors associated with ALDH2-deficiencies could be implemented in high-risk communities. A meta-analysis proved brief alcohol-control intervention programs to be effective in patients evident through 6 and 12 month check-ups and showed a mean decrease of approximately four drinks (-38g alcohol) per week in participants (Bertholet, 2005). Training programs for bar employees could also be utilized, so they are aware of the warning signs of alcohol-flushing and can limit individuals from over-drinking. Finally, diagnostic testing for ALDH2 (such as the questionnaire mentioned in the methodology section) could be implemented during regular physicals, as early detection of ALDH2 deficiencies can cause individuals to be more proactive about their drinking levels.
As cancer, cardiovascular disease, and AD are some of the leading causes of mortality in Eastern Asia, addressing risk factors that heighten the likelihood of developing these conditions is extremely crucial. With increased levels of awareness, preventative efforts can be taken in ALDH2-deficient individuals to reduce overall alcohol intake and decrease the potential long-term health consequences that come with alcohol-flushing.

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