Alcohol Consumption, *Aldehyde Dehydrogenase 2* Gene Polymorphisms, and Cardiovascular Health in Korea

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Alcohol consumption is a serious health issue in Korea in terms of the amount consumed and the behavior related to its consumption. Aldehyde dehydrogenase 2 (ALDH2) is a key enzyme in alcohol metabolism that degrades acetaldehyde to nontoxic acetic acid. The enzyme is coded by the *ALDH2* gene, which is commonly polymorphic in East Asian populations. A point mutation in the *ALDH2* gene (the rs671 allele) yields an inactive form of ALDH2 that causes acetaldehyde accumulation in the body after alcohol consumption, thereby inhibiting normal alcohol metabolism. Individuals who are homozygous for polymorphism in *ALDH2* tend to refrain from drinking alcohol, decreasing their chances of developing alcoholism and exposure to the associated risks. Mendelian randomization (MR) studies have demonstrated that alcohol consumption predicted by *ALDH2* genotype is causally related to cardiovascular risks. Moreover, recent MR studies suggest that the *ALDH2* variant has mechanistic effects on some disease outcomes or mortality through increased blood levels of acetaldehyde, showing differences therein between heterozygotes (*ALDH2*2*2*) and homozygotes (*ALDH2*1*2*) in those who consume alcohol. Accordingly, consideration of *ALDH2* genotype in alcohol prevention programs is warranted. In conclusion, strategies that incorporate genetic information and provide an evidential basis from which to help people make informed decisions on alcohol consumption are urgently required.

Key Words: Alcohol, aldehyde dehydrogenase 2, Mendelian randomization analysis, guidelines

INTRODUCTION

In Korea, alcohol abuse is a serious health issue in terms of the amount consumed and behaviors related to its consumption.[1] According to the Korea National Health and Nutrition Examination Survey (KNHANES) 2013,[2] the percentage of individuals that consumed alcohol at least once a month comprised approximately 55% in 2005 and 60% in 2013, showing an increasing trend. Heavy drinkers (those who consume at least three glasses of alcohol per day) reportedly accounted for one in four men, while men in their 40s and 50s exhibited the highest alcohol abuse and dependency rates. In addition, the KNHANES revealed that the high-risk drinking rates by sex, as well as the proportion of youths exposed to alcohol, have gradually increased.[2]

It is generally accepted that alcohol abuse has negative effects on health and quality of life; thus, guidelines for the regulation of alcohol consumption at a global level have been suggested. An example of this would be the "Global Strategy to Reduce the Harmful Use of Alcohol" proposed by the World Health Organization.[3] In the United States, alcohol prevention programs and services, such as AlcoholEdu and Project ALERT, have been initiated to regulate alcohol-associated risks.[4] In Korea, however, although an age limit for alcohol consumption is in effect, there are no specific regulations on the time and place of alcohol sales. Moreover, South Korea has no national agency or independent research institution for developing guidelines and policies on alcohol consumption. The absence of a detailed national policy on alcohol consumption in Korea has led to a culture of binge drinking and an increase in the

incidence of alcohol-related accidents. Therefore, we find it necessary to focus on the control of alcohol abuse in this population.

It has been suggested that individual alcohol sensitivity and its influence are affected by genotype. The *aldehyde dehydrogenase* (*ALDH2*) gene encodes the major enzyme responsible for alcohol metabolism, which eliminates acetaldehyde.[5] The *ALDH2* gene is polymorphic in East Asians, including Koreans, and influences blood levels of acetaldehyde and behavior after consumption, which is associated with the risk for alcoholic cirrhosis, cardiovascular disease (CVD), and cancer.[6-10] The *ALDH2* polymorphism is associated with a flushing response to alcohol use and lowers alcohol consumption, which acts as protective factors for CVDs.[6,11] A previous study has reported that *ALDH2*2* homozygotes and heterozygotes had 18 and 5 times higher blood alcohol levels, respectively, than *ALDH2*1* homozygotes after drinking the same amount of alcohol.[12] Thus, it has been suggested that intervention for alcohol use should be individually specified, considering genotype information. In this review, we highlight the role of *ALDH2* polymorphisms in alcohol-related health problems in Koreans. We also propose an educational model incorporating genetic information on ALDH2 that may improve alcohol consumption-related behaviors in this population.

ALCOHOL: A MAJOR PREVENTABLE RISK FOR HEALTH PROBLEMS

A number of epidemiologic studies have found that alcohol intake has both positive and negative effects on cardiovascular health. It has been generally reported that high alcohol intake is a risk factor for diabetes and CVDs.[13,14] On the other hand, other epidemiological evidence have suggested that moderate alcohol consumption might have a protective effect against chronic diseases, reflected in the so-called J-shaped association.[15] However, the results of observational studies have limitations because they are affected by confounding variables or reverse causation when investigating the association between alcohol consumption and the risk for chronic diseases.[16] For example, people who stopped drinking, used as a control for moderate drinkers, may do so because of health problems, indicating reverse causation. In supporting this, Ng Fat, et al.[17] confirmed that poor health directly influenced nondrinking throughout the life course, indicating a sick-quitter bias. Consistently, a recent meta-analysis[18] found that a reduction in mortality risk in moderate drinkers (one to two glasses a day) was not supported when they were compared with intermittent drinkers (at most one glass a week/intake of less than 1.3 g per day) or those who never drank. In other words, the lower mortality risk in intermittent drinkers can be explained by reverse causation or confounding variables, rather than by the amount of alcohol intake. Hence, it is difficult to conclude that lowering

alcohol intake reduces mortality. Furthermore, it has also been reported that there is no association between limited alcohol intake and cancer- or cardiovascular-related mortality[19] and that even moderate drinking can be harmful.[20] For these reasons, the International Agency for Research on Cancer classified alcohol as a Group 1 carcinogen,[21] while the European Union enhanced their cancer prevention guidelines to include "no alcohol drinking" in 2014.[22] Following these global recommendations, the Ministry of Health and Welfare of South Korea revised their guidelines in March 2016 to "To prevent cancer, drinking even small amounts of alcohol (one or two glasses a day) should be avoided," which was previously "Drinking up to two glasses a day".[23] The results of a recent meta-analysis in South Korea also showed that moderate alcohol intake has no beneficial effect on total mortality,[19] supporting current considerations to extend the application of this drinking guideline to other chronic diseases, such as stroke. However, data are scarce on the relationship between alcohol consumption and chronic diseases, such as diabetes and CVD, in Korea, and information on safe levels of alcohol consumption for diseases of interest is hard to find. Thus, it is necessary to accumulate scientific evidence on the effects of alcohol consumption on health outcomes in order to establish a health policy that promotes a desirable alcohol intake and drinking pattern in this population.

THE EPIDEMIOLOGY OF GENETIC DIFFERENCES IN ALCOHOL USE: *ALDH2* AS A GENETIC MARKER FOR ALCOHOL CONSUMPTION

Alcohol consumption behavior is considered to reflect complex etiology, involving environmental (e.g., cultural, social, and political) and genetic factors.[24-26] Although some studies of alcohol use support this general understanding,[27,28] there is evidence that genetic variations, such as *ALDH2*2* and *alcohol dehydrogenase 1B (ADH1B)*2*, have measurable effects on alcohol consumption in East Asians.[29-31] Consistently, a genome-wide association study in a Korean population identified genetic loci associated with alcohol intake.[32] According to this report, genes, including *C12orf51*, *CCDC63*, *MYL2*, *OAS3*, *CUX2*, and *RPH3A*, are in high linkage disequilibrium (LD) with the *ALDH2* gene and are associated with amounts of alcohol consumed. Particularly, a genetic polymorphism in *C12orf51* (rs2074356) at 12q24.13, which was in substantial LD with several intronic single nucleotide polymorphisms in *ALDH2*, such as rs2238151, showed the highest correlation with alcohol consumption and was associated with delayed acetaldehyde catabolism.[33] Another study in a Korean population reported that *ADH1B*47Arg* and *ALDH2*487Glu*, which affect alcohol metabolism, explained 86.5% of Korean alcoholics.[34] This study also suggested that individuals who have

the *ADH1B*47Arg* allele and the susceptible *ALDH2*487Glu* allele at either loci had 11 times greater risk for alcoholism. Based on these observations, it is possible that these two genes, which are closely related to alcohol metabolism, could well explain the reason for alcohol intake and the probability of becoming an alcoholic in Koreans. Several genetic polymorphisms in *ADH1B* and *ALDH2* reportedly generate functional differences in the activities of enzymes involved in alcohol metabolism, which influence the level of acetaldehyde, an intermediate metabolite of alcohol in the body. Generally, *ALDH2* variation has a strong effect on alcohol metabolism, affecting blood levels of acetaldehyde to a greater extent than *ADH1B* (Fig. 1A)[29,35,36] A study in a Korean population reported the lack of a significant association between the *ADH1B* genotype and self-rating of the effects of alcohol.[36] In line with this, a previous study in Asian-Americans also showed that the *ALDH2*2* variant had a protective effect on alcohol use behavior, whereas the *ADH1B* variant was not associated with alcohol consumption.[35] However, this requires further confirmation in other populations. Additionally, in East Asian populations (Chinese, Japanese, Korean, and Thai), the possession of two *ALDH2*2* alleles was associated with a nine-fold reduction in alcohol consumption, whereas the possession of two *ADH1B*2* alleles was associated with a five-fold reduction.[29] Thus, particular attention has been focused on the roles of genetic variants in *ALDH2* in alcohol metabolism. Interestingly, reports show that up to 50% of East Asians[9,37,38] and about 25–35% of Koreans have an inactive form of ALDH2,[39,40] which is scarce in North Americans or Europeans (Fig. 1B). The inactive form of ALDH2 due to genetic variation causes the accumulation of acetaldehyde in the body, which leads to physiologic adverse effects, such as flushing,
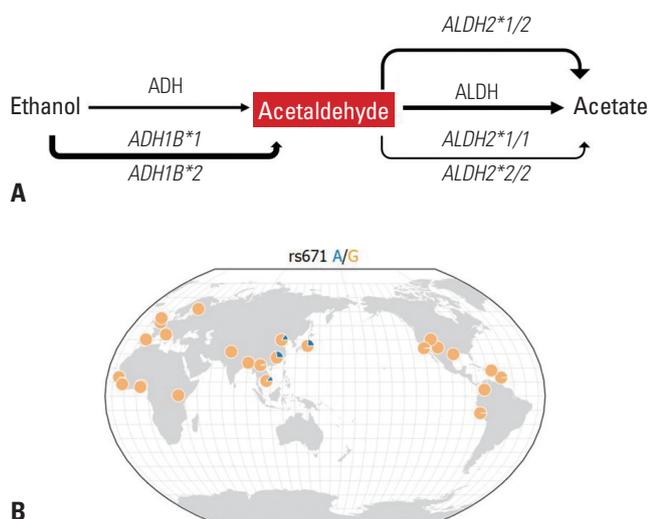
palpitations, headache, and displeasure,[41] as well as a behavioral influence in refraining from alcohol consumption. This genetically chosen behavior helps lower the chances of being alcoholic and reduces exposure to its associated risks. In this regard, several studies have proposed the use of *ALDH2* as a biomarker for alcoholism.[41,42]

ACETALDEHYDE METABOLISM, PHYSIOLOGICAL RESPONSES, AND HEALTH EFFECTS OF *ALDH2* VIA ALCOHOL CONSUMPTION ACCORDING TO *ALDH2* VARIANTS

Numerous studies have reported differences in alcohol metabolism, physiological functions, and drinking behavior according to the rs671 genetic polymorphism. Specifically, heterozygous individuals (*ALDH2*1/*2*) exhibit slower acetaldehyde degradation rates, equating to markedly higher levels of acetaldehyde than in homozygotes (*ALHD2*1/*1*),[5] which was also verified in Koreans.[43,44] It is generally accepted that high acetaldehyde levels in the blood exert negative effects on cardiovascular functions, causing subsequent elevations in heart rate, cardiac output, and blood flow velocity in the facial artery.[45] Also, the accumulation of acetaldehyde over time induces various symptoms, including facial flushing.[46] According to a survey of 250 Thai people,[47] 80% of those with the *ALDH2*1/*2* genotype responded that they experienced flushing immediately after drinking alcohol. In contrast, only 28% of those with the *ALDH2*1/*1* genotype answered that they experienced flushing immediately after alcohol consumption. This was further supported by a clinical study[48] showing that the *ALDH2*1/*2* genotype raised the heart rate and induced facial flushing in

Fig. 1. Alcohol metabolism according to genetic polymorphisms. (A) Aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1B (ADH1B) are involved in alcohol metabolism. Generally, *ALDH2* variants have a greater influence on alcohol intake than *ADH1B* variants in East Asians. (B) *ALDH2* variants mainly exist in East Asian populations. Adapted from Cho, et al. Sci Rep 2015;5:18422.[6]
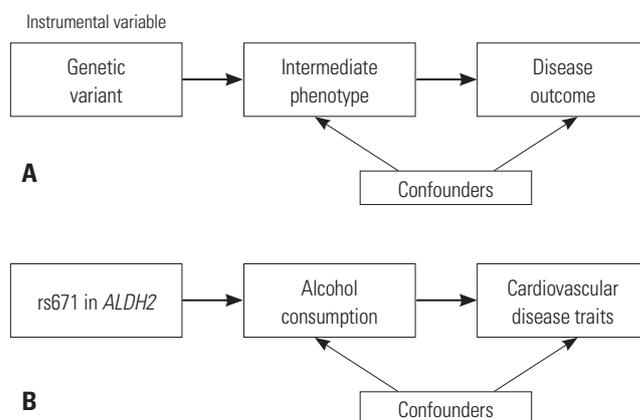

Fig. 2. Scheme of the Mendelian randomization approach. The scheme of the Mendelian randomization approach. (A) This method uses a genetic variant, which proxies for exposure that is expected to be related to the outcome. (B) Using the Mendelian randomization approach, the causal effects of alcohol intake on cardiovascular outcomes can be investigated while controlling confounders and reverse causation. *ALDH2, aldehyde dehydrogenase 2.*

individuals after alcohol consumption relative to those with the *ALDH2*1/*1* genotype. Moreover, there is also evidence that the *ALDH2*1/*2* genotype aggravates psychomotor functions relative to the *ALDH2*1/*1* genotype in Koreans.[49,50]

While people with the inactive form of ALDH2 tend to refrain from alcohol consumption, thus decreasing their exposure to associated risks, the inactive form of ALDH2 also manifests negative effects on health because of the toxicity of accumulated acetaldehyde after drinking. So far, studies on an ALDH2 variant (the rs671 allele) have suggested that an alteration in ALDH2 activity caused by genetic variation is associated with a 20–60% increase in susceptibility to CVD and cancer in Asians.[51-54] However, previous studies have not considered the possible association between alcohol drinking behavior caused by the ALDH2 variant and CVD.[55] Similarly, associations observed by Gu and Li[52] and Wang, et al.[53] between the *ALDH2*504lys* allele and increased risk of myocardial infarction were based on ordinary least square estimates. In addition, an association study in a Chinese population reported that the *ALDH2 Glu504Lys* polymorphism was associated with the risk for hypertension in men, but not in women, who consumed relatively lower amounts of alcohol independent of their genotype.[54] Such a difference in the association between men and women provides evidence that the *ALDH2* polymorphism influences outcomes only through alcohol intake.[56] This is in line with recent studies showing that lower alcohol intake in individuals with the rs671 A allele, compared to wild-type homozygotes,[57,58] was associated with reduced cardiometabolic diseases, glucose levels, and blood pressure in men, who generally consumed more alcohol than women.

It was recently reported that Koreans with the inactive form of ALDH2 had a higher incidence of myocardial infarction due to the accumulation of acetaldehyde.[59] However, alcohol intake had not been taken into account in the evaluation of the association between ALDH2 and CVD. Additionally, another study in the Korean population reported a 52% lower incidence of lung cancer in nondrinkers with the inactive form of ALDH2 than those without.[60] Based on evidence that *ALDH2*2*2* homozygotes consume considerably less alcohol than the wild-type homozygotes (*ALDH2*1*), with heterozygotes consuming intermediate amounts,[8] it might be more reasonable to consider *ALDH2* as a proxy for alcohol intake when investigating the effect of *ALDH2* variants on CVD outcomes.

MENDELIAN RANDOMIZATION ANALYSIS BASED ON *ALDH2* POLYMORPHISMS

Recently, our research group tested whether alcohol intake is associated with cardiovascular risks in the Korean population, using genetic variation in *ALDH2* (rs671) as a proxy for alcohol intake, in a MR framework (Fig. 2).[6] We demonstrated, for

the first time in a Korean population, a causal relationship between alcohol intake and hypertension and several cardiometabolic risk factors using an MR method that eliminated interference by confounders.[61] Many epidemiologic studies have shown that moderate alcohol intake protects individuals against CVDs, as reflected by the J-shaped correlation,[15] are limited by confounding variables, including smoking and socioeconomic position, and reverse causation due to the characteristics of observational studies. For example, light or moderate alcohol users also tend to have other characteristics that are particularly beneficial to health, such as high income levels, good education, and regular exercise (confounding). Also, people diagnosed with chronic diseases tend to change their alcohol consumption patterns over time (reverse causation). In our previous study utilizing the MR framework,[6] we found that the amount and pattern of alcohol intake are influenced by genotype and are associated with an increased risk for CVDs in a dose-dependent manner throughout life. Our findings are consistent with those of a study using the MR method in Chinese individuals,[11] which showed that alcohol intake is predicted by genetic polymorphisms in *ALDH2* and has negative effects on blood pressure and blood triglyceride levels. It has yet to be determined whether the effects of genetic polymorphisms in *ALDH2* on risk factors for CVD shown in our study, as well as those in other populations, are caused by the physiologic effects of these genetic variations or a subsequent result of alcohol intake (Table 1). A recent study in South Korea showed that genetic polymorphisms in *ALDH2* are correlated with stroke in men only,[62] raising the possibility that the observed association is mainly attributable to the strong correlation mediated by alcohol intake, especially in men. Further, very recently, it has been suggested that alcohol flushing can be used as an instrumental variable to evaluate the health impact of alcohol consumption, since alcohol flushing is closely related to ALDH2 deficiency.[63] Using a phenotypic proxy of a genotype allows researchers to achieve MR-inspired causal inference even genetic data are absent.[64]

A GENETIC EDUCATION MODEL FOR ALCOHOL CONSUMPTION AND RELATED BEHAVIOR

According to a recent report in South Korea, the mortality rate of Korean men with chronic diseases, such as oral or laryngeal cancer, is approximately 30–40% and is attributable to alcohol consumption.[65] In order to reduce alcohol intake more effectively at the population level, novel personalized drinking guidelines incorporating genetic information, such as *ALDH2* variants, would be of value. It was previously reported that *ALDH2* variants increased the risk of head and neck cancer only with the interaction with drinking alcohol, and *ALDH2*1*2* heterozygotes showed a less severe reaction to alcohol but an

Table 1. Mendelian Randomization Studies on Alcohol Consumption Predicted by Genotype and CVD Risk Factors

Author	Population	Instrument	Outcome	Statistics	Major results
Jee, et al.[69]	Korean (n=2993 men and 1374 women)	rs671 in *ALDH2*	Serum glucose levels	Instrumental variable regression analysis	An increase of 1 unit of alcohol with the G allele of rs671 increased serum glucose levels in men.
Cho, et al.[6]	Korean (n=3365 men and 3787 women)	rs671 in *ALDH2*	Risk factors for CVD	Instrumental variable regression analysis	An increase of 1 unit of alcohol with the G allele of rs671 increased CVD risk factors, including blood pressure, waist-to-hip ratio, fasting blood glucose, and TG levels.
Xu, et al.[70]	Chinese (n=2321 men and 2757 women)	rs671 in *ALDH2*	Gamma-glutamyltransferase	Instrumental variable regression analysis	An increase of 1 unit of alcohol with the G allele of rs671 increased gamma-glutamyltransferase by 10.60 U/L per 10 g ethanol/day.
Au Yeung, et al.[71]	Chinese (n=4588 men)	rs671 in *ALDH2*	Heart rate	Instrumental variable regression analysis	An increase of 1 unit of alcohol with active *ALDH2* was associated with an increase in heart rate of 0.98 beats per minute.
Au Yeung, et al.[72]	Chinese (n=4867 men)	rs671 in *ALDH2*	Self-reported CVD and biologic CVD risk factors	Instrumental variable regression analysis	An increase of 1 unit of alcohol with the G allele of rs671 was associated with an increase in HDL cholesterol per alcohol unit, and DBP, LDL cholesterol, TG, or glucose, and the prevalence of self-reported CVD.
Au Yeung, et al.[73]	Chinese (n=4707 men for alcohol consumption was not associated with delayed 10-word recall score; 2284 men for MMSE score)	rs671 in *ALDH2*	Cognitive function	Instrumental variable regression analysis	An increase of 1 unit of alcohol with the G allele of rs671 was not associated with delayed 10-word recall score or MMSE score.
Tabara, et al.[74]	Japanese (n=2756 men and 5608 women)	*ALDH2*	LDL/HDL cholesterol levels	Linear regression analysis with an additive genetic model	The *ALDH2*1* variant was strongly associated with higher alcohol consumption in men. The *ALDH2*1* appeared causally related to increased HDL cholesterol levels in men. The *ALDH2* variant also related to decreased total LDL cholesterol levels, while the LDL profiles were worsened.
Tabara, et al.[75]	Japanese (n=2289 men and 1940 women)	*ALDH2*	LDL/HDL cholesterol levels	Linear regression analysis with an additive genetic model	The *ALDH2*1* variant was strongly associated with higher alcohol consumption in men. The *ALDH2*1* appeared causally related to increased HDL cholesterol levels and reduced LDL cholesterol levels in men. Alcohol consumption was related to not only increased HDL cholesterol levels but also decreased LDL cholesterol levels and particle numbers.
Taylor, et al.[11]	Chinese (n=1712 diabetes cases and 2076 controls)	rs671 in *ALDH2*	Cardiovascular and metabolic factors	Linear regression analysis with an additive genetic model	The A allele of rs671 was strongly associated with reduced alcohol use in men and women. The A allele was associated with lower blood pressure, lower HDL cholesterol and lower triglycerides in men.

ALDH2, aldehyde dehydrogenase 2; CVD, cardiovascular disease; DBP, diastolic blood pressure; LDL, low-density lipid; HDL, high-density lipid; TG, triglyceride; MMSE, Mini-Mental State Examination.
The table only includes Mendelian randomization studies based on instrumental variable (IV) regression using rs671 in *ALDH2* as an instrument. Papers included in Table 1 were collected from MEDLINE (http://www.ncbi.nlm.nih.gov/PubMed) using the following keywords: "Aldehyde dehydrogenase 2" and "ALDH2" in combination with "Mendelian randomization" and "alcohol." The abstracts of the collected articles were scanned for inclusion of any cardiovascular-related outcomes of interest. We searched for all papers published before January 2017. The minimum requirement for inclusion was Mendelian randomization analysis using *ALDH2* as an instrument. We excluded meta-analyses, because they did not perform IV regression analysis directly. Among the 20 papers identified by the search strategy, irrelevant articles (n=7) and meta-analyses (n=4) were excluded. When sufficient information could not be obtained, the study was excluded.

elevated risk for cancer with the same amount of alcohol.[8] In support of this, an animal study demonstrated that maternal deficiency in ALDH2 due to the *ALDH2*2* allele resulted in extensive developmental malformations, particularly in cases of alcohol consumption during pregnancy. They also reported that genotoxic aldehydes in *ALDH2*2* homozygous fetuses born from *ALDH2*2* homozygous or heterozygous mothers who consumed alcohol were continuously accumulated, possibly resulting in birth defect.[66] Given that approximately 30% of the Korean population are genetically deficient in *ALDH2*,[6] it would be effective if people could be informed about their own genetic predisposition to enable them to identify their own cardiovascular risks. A previous study on Health Risk Appraisal Models, which made use of information on *ALDH2* variants to evaluate disease outcomes, supported this notion, showing high detection rate.[67] In line with this, the inclusion of genetic information is now regarded as a very useful tool for educating alcohol intake and drinking behavior properly in community and/or clinical settings,[68] yet still, such a genetic education model is not available in Korea.

CONCLUSION

Although about 30% of Koreans have the inactive form of ALDH2, alcohol intake rates are still high in Koreans. This genetically high-risk group represents a target for a customized alcohol-prevention program. In particular, the development of strategies using genetic information may prove necessary to modifying alcohol consumption behaviors in Korea. This novel approach is expected allow people to make informed decision about their own alcohol consumption and, ultimately, raise public awareness of alcohol-gene interactions that is associated with harmful drinking behavior and health outcomes.

ACKNOWLEDGEMENTS

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