NEW DIMENSION SERIES

Sustainable Development Goals (SDGs) for
Hypertension Zero in the era of Anthropocene.

CATEGORY B: HYPERTENSION AND DIVERSITY (HYPERTENSION & GENETIC ANCESTRY)

Diversity of Aldehyde Related Diseases: Learning from Aldehyde Dehydrogenase 2 (ALDH2) Polymorphism —Alcohol Intake, Flushing/Intolerance and Hypertension

YUJI MIZUNO[1, 2] AND HIROSHI ITOH (ISH VICE PRESIDENT)[3]

[1] Mizuno Heart Clinic: Koshi city, Kumamoto, Japan
[2] Kumamoto Aging Research Institute: Kumamoto city, Kumamoto, Japan
[3] The Center for Preventive Medicine, Keio University, Japan

Alcohol (ethanol) flushing syndrome (AFS) including facial flushing, headache, nausea, and palpitation in response to a small amount of alcohol intake is common among East Asians but is almost absent in other populations.[1] AFS, therefore, is also called Asian flushing syndrome. Ethanol is metabolized to acetaldehyde by alcohol dehydrogenase subunit beta (ADH1B) and then to acetic acid by aldehyde dehydrogenase 2 (ALDH2).[1] There are polymorphisms in human ALDH2 genes, and the carriers of variant ALDH2 or ALDH2*2 (Glu504Lys) genotype have a severely reduced enzymatic activity, compared to wild ALDH2, ALDH2*1.[2] The carriers of these variant genes manifest AFS on alcohol intake due to an accumulation of acetaldehyde.[3] Approximately 40% of Japanese have ALDH2*2 genotype. Attenuation of ALDH2 activity increases the levels of acetaldehyde and other reactive aldehydes and induces oxidative stress because mitochondrial ALDH2 reduces the reactive oxygen species (ROS) formation related to toxic aldehydes[1] **(Figure 1)**.

Coronary spasm is an important and common disease in cardiology. Coronary spasm is prevalent among East Asians, including those in Japan, but not in the Western populations.[4] The survey on the prevalence of CSA at multi-institutions in Japan showed that CSA was documented in 921 (40.9%) of the 2251 consecutive patients with angina pectoris who underwent coronary angiography.[5] Thus, there seems to be a racial difference in the prevalence of coronary spasm between East Asians (Japanese) and Caucasians.[4] We reported that the rate of coronary spastic angina (CSA) was significantly increased in patients with ALDH2*2 genotype.[6] We further presented that ALDH2*2 genotype is a causative risk factor for ST elevated myocardial infarction (STEMI) in Japanese patients according to Mendelian randomization.[7]

ALDH2 removes not only acetaldehyde but also other toxic aldehydes, including 4- hydroxy-2-nonenal (4-HNE) and malondialdehyde from lipid peroxidation or acrolein in tobacco smoke, and thereby protects tissues and cells from oxidative damage.[1] Conversely, ALDH2 activity is suppressed by ROS and/or aldehydes.[2] It is thus likely that

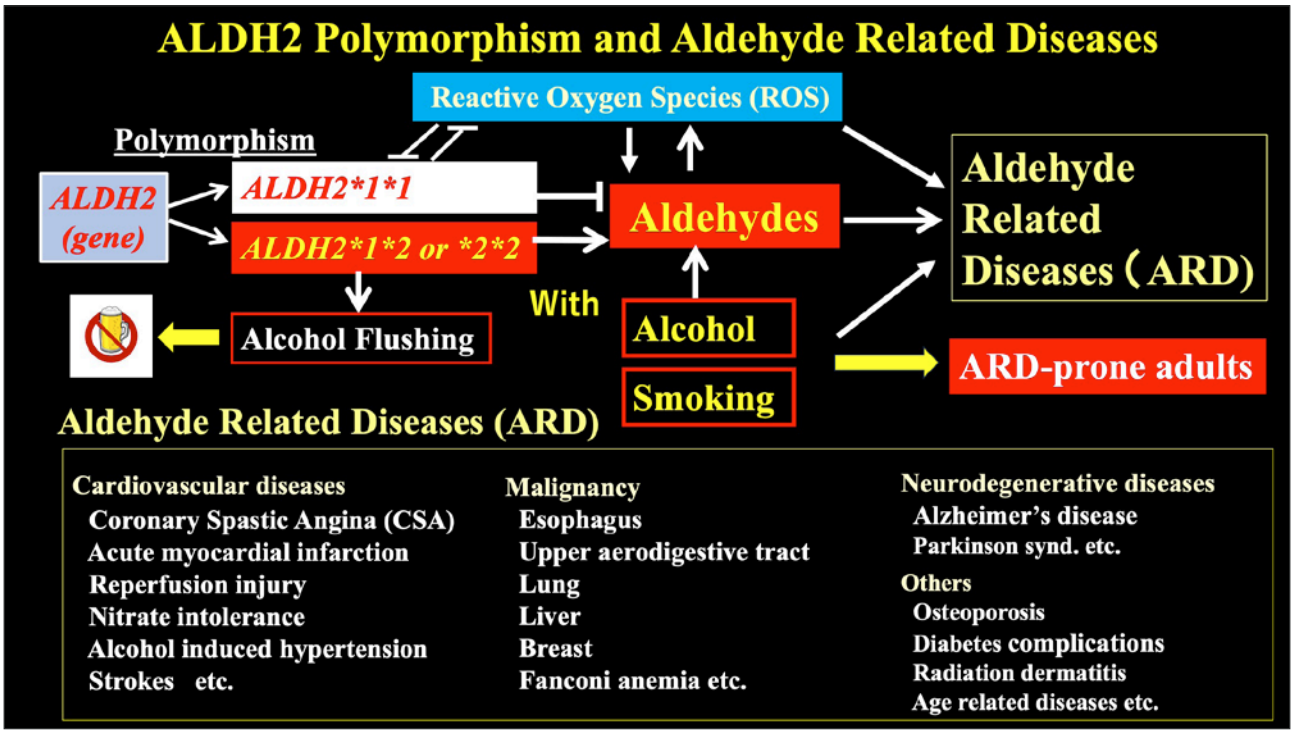

Figure 1

carriers of ALDH2*2 have increased reactive aldehydes as risk factors for coronary spasm and AMI.[6,7] We also reported that reperfusion injury in AMI is more severe in the carriers of ALDH2*2, that is, ALDH2*1*2 or ALDH2*2*2, compared to ALDH2*1*1.[7] ALDH2 may thus possess important therapeutic potential against alcoholic and other forms of myocardial damage as well.[1]

Toxic aldehydes, which increase in carriers of ALDH2*2, are also important carcinogens. Many cancers are induced and the incidence rates of various cancers, especially upper aerodigestive tract cancers, are amplified by smoking and alcohol drinking significantly in carriers with ALDH2*2.[1] Considering that cigarette smoke is also a source of toxic aldehyde, it is not surprising that smoking and heavy drinking combined with ALDH2*2 genotype carry the greatest cancer risk; indeed, ALDH2*2 carriers are frequent in the youngest patients with esophageal cancer.[1] Many diseases such as various cancers, Fanconi anemia, CSA, AMI, nitroglycerin tolerance, diabetic complications (via formation of advanced glycation end products, AGEs), osteoporosis, Parkinson syndrome, neurodegenerative diseases including Alzheimer's disease[1] could be called Aldehyde Related Diseases (ARD)". We should take great care for ARD when treating in patients for the carriers with ALDH2*2 allele. The carriers with ALDH2*2 allele are considered to have high risk for having complications with multiple ARD, especially with alcohol drinking and/or smoking. They can be considered to be "ARD-prone adults" **(Figure 1)**.

In contrast, there is an important and interesting report that ALDH2*2 genotype is a significant genetic factor for male longevity of more than 90 years in Koreans.[8] This observation suggests a possible intriguing significance of ALDH2 gene as a double-edged sword. It is inferred that ALDH2*2 genotype is thought to have favorable influence for survival in history of evolution for people living in rice-growing regions, since aldehydes may protect against infectious diseases, including parasite-born diseases, that are common in rice-growing regions. Further research is required in the diversity of genetic ancestry of this gene. In addition, there raised the possibility that the lack of ALDH activity could develop other protective pathways against ROS. It is reported that transgenic mice overexpressing ALDH2*2 induced mitochondrial aldehyde stress and subsequent stimulation of tolerance to oxidative stress with the increase of intracellular glutathione levels and pentose phosphate pathway (metabolic remodeling) in the heart.[9] This compensatory mechanism was also demonstrated in Tetralogy of Fallot patients with ALDH2*2 who exhibited more depressed ALDH2 activity in cyanosis with the

increase of glutathione level and shown to exert cardio-protection[10] Attenuated ALDH2 activity and increase of toxic aldehydes could strengthen other defense mechanisms against stresses ("Hormesis") on some occasions and may be related partially to longevity of Japanese.

As for the relationships between ALDH2 genotypes and hypertension, a meta-analysis including 19,608 subjects found that ALDH2*2 was the most crucial SNP related to the blood pressure variation in East Asians.[11] ALDH2*2 genotype presented low levels of both systolic and diastolic blood pressure compared with those of wild type[11] Considering that ALDH2 encodes the crucial enzyme involved in ethanol metabolism, its effect on blood pressure could be tightly associated with alcohol intake. Ethanol and/or acetaldehyde are known to activate sympathetic activity, stimulate the expression of angiotensin II type 1 receptor or impair endothelial nitric oxide activity for elevation of vascular tone and promotion of vascular remodeling, which could contribute to high blood pressure and its complications.

It is well recognized that individuals with ALDH2*2 mutation tend to limit or even abstain from alcohol intake due to the adverse effects such as facial flushing and palpitation[12] **(Figure 1)**. Ota et al. reported that by analyzing 1,225 male Japanese workers, the genotype frequencies of ALDH2 genetic polymorphism were 62.3, 32.4 and 4.7% for *1*1, *1*2 and *2*2, respectively. ALDH2 *1*1 group consumed a significantly higher amount of alcohol with more elevated alanine aminotransferase (ALT) and aspartate transaminase (AST), and exhibited significantly higher blood pressure, compared to ALDH2 *1*2 or 2*2 group (125.5±13.7 mmHg vs 122.2±13 mmHg in systolic and 78.6±81 mmHg vs 76.0±11.0 mmHg in diastolic blood pressure; mean ± SD). There was a positive relation between systolic blood pressure and the amount of daily alcohol intake in ALDH2 *1*2 or 2*2 group.[13]

Although the enzymatic activity of ALDH2*1*2 is less than 20% of *1*1, because of the dominant effect of ALDH2*2, the average alcohol intake of ALDH2*1*2 is around 70% of ALDH2*1*1, and 10-20% of alcoholics are ALDH2*2 carriers,[14,15] indicating that alcohol drinking behavior is determined by other additional factors, including the polymorphism of ADH1B, since blood acetaldehyde concentration is mainly determined by the activities of ADH1B and ALDH2.[16]

Alcohol drinkers with ADLH2*2 genotype are demonstrated to have high risk for ARD, such as alcoholic liver diseases or macrocytic anemia.[17] ALDH2*2 genotype, therefore, generates ARD at high probability and in great severity, in combination with the enormous aldehyde suppliers, including smoking as well as alcohol **(Figure 1)**. In precision medicine, ARD-prone adults should be strongly counselled to quit smoking and alcohol and take special attention for medical care.

References

1. Chen CH, Ferreira JC, Gross ER, Mochly-Rosen D, Targeting aldehyde dehydrogenase 2: new therapeutic opportunities. Physiol Rev 2014; 94:1–34

2. Li YY, Wang H, Wu JJ, Kim HJ, Yang XX, Geng HY, Gong G ALDH2 gene G487A polymorphism and coronary artery disease: a meta-analysis including 5644 participants. J Cell Mol Med 2018; 22:1666–1674

3. Crabb DW, Edenberg HJ, Bosron WF, Li TK. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2(2) allele is dominant. J Clin Invest 1989; 83:314–316

4. Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y. Coronary artery spasm—clinical features, diagnosis, pathogenesis, and treatment. J Cardiol 2008; 51:2–17

5. Yasue H, Sasayama S, Kikuchi K, Okumura K, Matsubara T, Miwa K, Gotoh Y, Shimokawa H, Yokoyama M, Yokoyama H, Nakamura Y, Kawada M, Inoue K, Nakamura K. The study on the role of CAS in ischemic heart disease. In: Annual report of the research on cardiovascular diseases 2000. National Cardiovascular Center, Osaka, 2000; pp 96–97 (in Japanese)

6. Mizuno Y, Harada E, Morita S, Kinoshita K, Hayashida M, Shono M, Morikawa Y, Murohara T, Nakayama M, Yoshimura M, Yasue H. East Asian variant of aldehyde dehydrogenase 2 is associated with coronary spastic angina: possible roles of reactive aldehydes and implications of alcohol flushing syndrome. Circulation 2015; 131:1665–1673

7. Mizuno Y, Hokimoto S, Harada E, Kinoshita K, Nakagawa K, Yoshimura M, Ogawa H, Yasue H. Variant aldehyde dehydrogenase 2 (ALDH2*2) is a risk factor for coronary spasm and ST-segment elevation myocardial infarction. J Am Heart Assoc 2016a; 5:pii: e003247

8. Park JW, Ji YI, Choi YH, Kang MY, Jung E, Cho SY, Cho HY, Kang BK, Joung YS, Kim DH, Park SC, Park J. Candidate gene polymorphisms for diabetes mellitus, cardiovascular disease and cancer are associated with longevity in Koreans. Exp Mol Med. 2009;41:772-781

9. Endo J, Sano M, Katayama T, Hishiki T, Shinmura K, Morizane S, Matsuhashi T, Katsumata Y, Zhang Y, Ito H, Nagahata Y, Marchitti S, Nishimaki K, Wolf AM, Nakanishi H, Hattori F, Vasiliou V, Adachi T, Ohsawa I, Taguchi R, Hirabayashi Y, Ohta S, Suematsu M, Ogawa S, Fukuda K. Metabolic remodeling induced by mitochondrial aldehyde stress stimulates tolerance to oxidative stress in the heart. Circ Res 2009 ;105:1118-1127

10. Zhang H, Gong DX, Zhang YJ, Li SJ, Hu S. Effect of mitochondrial aldehyde dehydrogenase-2 genotype on cardioprotection in patients with congenital heart disease. Eur Heart J. 2012; 33:1606-1614

11. Kato N, et al. Meta- analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nat Genet. 2011; 43:531-8

12. Takeshita T, Yang X, Morimoto K. The ALDH2 genotype, alcohol intake, and liver-function biomarkers among Japanese male workers. Hum Genet 2000;106:589-593

Yuji Mizuno – aldh2@icloud.com

Hiroshi Itoh – hiito@keio.jp

13. Ota M, Hisada A, Lu X, Nakashita C, Masuda S, Katoh T. Associations between aldehyde dehydrogenase 2 (ALDH2) genetic polymorphisms, drinking status, and hypertension risk in Japanese adult male workers: a case-control study. Environ Health Prev Med. 2016;21:1-8

14. Higuchi S, Matsushita S, Murayama M, Takagi S, Hayashida M. Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism. Am J Psychiatry 1995;152:1219-1221

15. Yokoyama A, Tsutsumi E, Imazeki H, Suwa Y, Nakamura C, Yokoyama T. Polymorphisms of alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 and the blood and salivary ethanol and acetaldehyde concentrations of Japanese alcoholic men. Alcohol Clin Exp Res. 2010;34:1246-1256

16. Tanaka F, Shiratori Y, Yokosuka O, Imazeki F, Tsukada Y, Omata M. Polymorphism of alcohol-metabolizing genes affects drinking behavior and alcoholic liver disease in Japanese men. Alcohol Clin Exp Res 1997 ;21:596-601

17. Yokoyama A, Yokoyama T, Brooks PJ, Mizukami T, Matsui T, Kimura M, Matsushita S, Higuchi S, Maruyama K. Macrocytosis, macrocytic anemia, and genetic polymorphisms of alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 in Japanese alcoholic men. Alcohol Clin Exp Res. 2014;38:1237-1246