Aldehyde Dehydrogenases Genetic Polymorphism and Obesity: From Genomics to Behavior and Health

Cheng Hu

Abstract Obesity is multifactorial and complex. Remarkable progress has been made recently in search for polygenic obesity through genome-wide association study (GWAS), but biology of polygenic effects on obesity is largely poor. This review summarizes the available evidence and provides an overview of the links between *ALDH2* variants and adiposity, which were firstly and mainly derived from studies of polygenic obesity and also indirectly investigated by using cell lines and mice. The genetic association studies have observed consistent associations of *ALDH2* variants with obesity-related traits including BMI, waist circumference (WC), waist-to-hip ratio (WHR), and visceral fat accumulation. In consideration of *ALDH2* variants with enzyme activity and alcohol consumption behavior in physiological mechanism studies, we proposed a model by which the physiological and behavioral consequences of alcohol consumption serve as an intermediary process between polymorphisms in *ALDH2* and obesity.

Keywords ALDH2 · Obesity · BMI · Central obesity · Variant

Abbreviations

4-HNE	4-hydroxykenals
ADH	alcohol dehydrogenase
ALDHs	aldehyde dehydrogenases
BMI	body mass index
FADE	FAt Distribution and diseasE

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GABA	γ-aminobutyric acid
GWAS	genome-wide association studies
IDF	International Diabetes Federation
PPAR-γ	peroxisome proliferator-activated receptor γ
ROS	reactive oxygen species
SFA	subcutaneous fat area
SGWAS	Shanghai Genome-Wide Association Studies
VFA	visceral fat area
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio

1 Introduction

Obesity, defined as an excessive fat accumulation, has increased at an alarming pace around the world. For the years 2013–2014, more than one-third (37.7%) of US adults have obesity, and the number is projected to 51% in 2030 [1]. Not only that, obesity is also a major heath concern in developing countries, where almost two in three of the world's people live with obesity. The rate of obesity has tripled since 1980 in the Middle East, the Pacific Islands, and China [2]. Obesity-related diseases such as type 2 diabetes, stroke, coronary heart disease, and some cancers have been the leading cause of disability and death. Clinically, overweight and obesity are quantified through the surrogate measure of body mass index (BMI), calculated as weight divided by the square of height. Individuals with a BMI of $\geq$28 kg/m^2 are considered obese and those with a BMI of 25 kg/m^2 to 29.9 kg/m^2 considered overweight according to World Health Organization (WHO) criteria [3]. The given BMI values indicate a higher percentage of body fat and metabolic disease risk for Asian populations than European populations; therefore, some Asian countries have revised the definition of obesity to adjust for ethnic differences [4]. In China, overweight and obesity are, respectively, identified as 24 kg/m^2$\leq$ BMI <28 kg/m^2 and BMI $\geq$28 kg/m^2 [5]. Central obesity (also known as visceral, android, apple-shaped or upper body obesity, abdominal obesity) can be clinically assessed by waist circumference (WC) which is highly associated with intra-abdominal fat. International Diabetes Federation (IDF) consensus defined central obesity in Europeans as a WC of $\geq$94 cm in males and $\geq$ 80 cm in females. Lower WC cutoffs are proposed for some ethnic groups (e.g., Chinese, Southeast Asians) [6]. Some indices corresponding to fat distribution, including waist-to-hip ratio (WHR), visceral fat are also used to assess central obesity.

Obesity is a product of the interaction between genetic factors and lifestyle risk factors (like smoking, drinking, lack of physical activity, sedentary, and Western diet). Even though surrounded by "obesogenic environment," a certain number of individuals could maintain their weight, suggesting genetic factors play a critical role in regulation of obesity. The advent of genome technology innovation (e.g., microarray and sequencing) has allowed far more detailed investigation of genetic

factors than previously known. Approximately 150 variants linked to obesity (e.g., BMI, WC, and WHR) have been identified through genome-wide association studies (GWAS) [7–24]. To be frustrated, little is known about the underlying mechanism by which those surprisingly high numbers of obesity-related variants imposed risk to obesity or body fat distribution. The interpretation of genomics to clinical care and public health is not enough, which requires the knowledge of genetic basis for obesity and interactions with health behaviors. Population research on the gene-environment interaction, which means that the sensitivity to environmental influences is regulated modulated by genetic factors, was still lacking.

The p.Glu504Lys (c.1510G>A, rs671) *ALDH2* missense variant is among numerous variants linked to obesity which reached the genome-wide significance. Aldehyde dehydrogenase 2 encoded by *ALDH2* is well known for most efficient enzyme of alcohol oxidation in the liver and other organs. Since alcohol consumption is also a public health concern, we focused on aldehyde dehydrogenases (ALDHs) genetic polymorphisms in this review and elucidated a genetic link to a common behavior and health.

2 Aldehyde Dehydrogenases

Human aldehyde dehydrogenases superfamily is a group of oxidizing enzymes responsible for the metabolism of endogenous and exogenous aldehydes. There are 19 functional isoforms with a wide range of tissue distribution, and some of them display specific subscapular compartments [25, 26]. Amino acid sequence similarities are about 40% between families and 60% or higher between the subfamilies. While some aldehydes functioned by ALDHs play key roles in normal physiological processes including vision, embryonic development, and neurotransmission, most of aldehydes can lead to cytotoxic damage. In this case, ALDHs are regarded as detoxification enzymes and serve as an important shield from the cytotoxic damage of aldehydes by converting them to their respective carboxylic acids.

Mitochondrial ALDH2 emerges as a particularly important enzyme for the oxidation of acetaldehyde in vivo, an immediate metabolite of alcohol. Alcohol-detoxifying pathway, specifically, consists of two-step enzymatic reaction. The first step is catalyzed by enzyme alcohol dehydrogenase (ADH), which converts alcohol to acetaldehyde. The second step is mainly catalyzed by ALDH2, dehydrogenating acetaldehyde into acetate to keep low levels of circulating acetaldehyde under normal condition. Any abnormal endogenous (i.e., mutations or liver disease) and exogenous (i.e., drugs) conditions which influence the enzyme activity could lead to the accumulation of acetaldehyde, manifested by a variety of unpleasant effects such as alcohol-flushing responses, nausea, vomiting, hypotension, or rapid heart rate. These unpleasant effects may prevent individuals from consuming more alcohol. Besides, it can also serve to remove lipid peroxidation-derived aldehydes and other reactive aldehydes to protect from the damage of excessive oxidative stress. Compelling evidence indicates that ALDH2 is a key mediator of endogenous cyto-

protection against ischemia injury [27, 28], gastrointestinal cancers [29, 30], late-onset Alzheimer's disease [31, 32], and a variety of human diseases.

The importance of ALDH2 proteins in physiological or pathological processes might be best evidenced by the associations between *ALDH2* functional variants and distinct disease phenotypes in humans. The p.Glu504Lys (c.1510G>A, rs671) *ALDH2* is the most common single point mutation in humans. This single point mutation occurs 35–45% among East Asians (approximately 560 million) but very rare in European populations [33]. The *ALDH2*2* (termed A allele) carriers have a lower ALDH2 enzymatic activity. *ALDH2*1/*2* heterozygotes are expected to have dramatically lower than 50% of the wild-type's enzymatic activity and *ALDH2*2/*2* homozygotes have <1–4% of the wild-type activity. Several large meta-analyses identified that carriers of the highly active *ALDH2*1* allele (or G allele) had an increased risk of alcoholism. rs886205 is another variant in the promoter region of *ALDH2* gene and was linked to ALDH2 activity through changing transcriptional activity in European populations.

3 The Associations Between Obesity and *ALDH2* Variants

3.1 What's for the GWAS of Obesity?

Multiple measurements including BMI, WC, WHR, and visceral fat area (VFA) are applied to quantify the degree of obesity. BMI, is a simple but standard measurement for overall obesity. Great advances in identification of variants linked to obesity can be largely attributed to the strategy of GWAS. The attempts to identify BMI-related variants are considered to facilitate some patterns of discovery for neuronal regulation in overall obesity [12, 16]. WC and WHR are considered as simple and commonly used markers for central obesity. Besides, other indices corresponding to fat distribution imaged by MRI or CT technology are superior to WC and WHR in terms of distinguishing between visceral fat and abdominal subcutaneous fat. The important thing for the central obesity-related variants has proven vital to elucidate the signals either shared with overall obesity or specific to central obesity.

3.2 The Link Between Obesity and ALDH2 *Variants*

The involvement of *ALDH2* in obesity and fat distribution was first suggested by GWAS in East Asian populations. So far, a total of three large-scale GWAS analyses and one replication study were performed among East Asian populations (as shown in Table 1) [21, 22, 34, 35]. The first GWAS analysis, published in *Nature Genetics* in 2009, uncovered a novel locus rs2074356 affecting WHR that reached

Table 1 The associations of *ALDH2* variants with obesity-related traits

SNP	Nearest gene	Chr	Position	Allele	EAF (%)	Traits	Effect sizes (SE)	*P* values	Date	References
rs2074356	*ALDH2-HECTD4*	12	112,207,597	C/T	0.85	WHRnoBMI	0.006 (0.001)	**7.8×10^{-12}**	2009	*Nature Genetics*
rs671	*ALDH2*	12	111,803,962	G/A	0.76	BMI	0.0378 (0.0057)	**3.4×10^{-11}**	2014	*Human Molecular Genetics*
rs12229654	*MYL2*	12	110,976,657	T/G	0.80	BMI	0.0341 (0.0058)	**4.56×10^{-9}**		
rs671	*ALDH2*	12	111,803,962	G/A	0.78	WCnoBMI	0.0482 (0.0089)	**6.73×10^{-8}**	2016	*Scientific Reports*
						WCadjBMI	0.0119 (0.005)	**0.0165**		
						WHRnoBMI	0.0255 (0.0089)	**0.0042**		
						WHRadjBMI	0.0062 (0.0078)	0.4220		
rs12229654	*MYL2*	12	110,976,657	T/G	0.83	WCnoBMI	0.0468 (0.0087)	**7.94×10^{-8}**		
						WCadjBMI	0.0174 (0.005)	**5.25×10^{-4}**		
						WHRnoBMI	0.0366 (0.0085)	**1.80×10^{-5}**		
						WHRadjBMI	0.0216 (0.0074)	**0.0035**		
rs671	*ALDH2*	12	111,803,962	G/A	0.78	BMI	0.2932 (0.1052)	**0.0053**	2016	*Scientific Reports*
						WCnoBMI	0.0075 (0.0015)	**4.05×10^{-7}**		
						WCadjBMI	0.0042 (0.0009)	**1.96×10^{-6}**		
						WHRnoBMI	0.002 (0.0009)	**0.0220**		
						WHRadjBMI	0.001 (0.0008)	0.2143		
						VFAnoBMI	0.036 (0.0075)	**1.94×10^{-6}**		
						VFAadjBMI	0.0224 (0.0057)	**9.64×10^{-5}**		
						VFA/SFAnoBMI	0.0177 (0.0069)	**0.0104**		
						VFA/SFAadjBMI	0.0164 (0.0068)	**0.0155**		
						SFAnoBMI	0.0042 (0.0061)	0.4953		
						SFAadjBMI	0.0006 (0.0043)	0.8827		

(continued)

Table 1 (continued)

SNP	Nearest gene	Chr	Position	Allele	EAF (%)	Traits	Effect sizes (SE)	*P* values	Date	References
rs2074356	*ALDH2-HECTD4*	12	112,207,597	C/T	0.85	BMI	0.1324 (0.1217)	0.2766		
						WCnoBMI	0.0035 (0.0017)	**0.0418**		
						WCadjBMI	0.002 (0.001)	**0.0477**		
						WHRnoBMI	0.0012 (0.001)	0.2157		
						WHRadjBMI	0.0008 (0.0009)	0.3860		
						VFAnoBMI	0.0219 (0.0087)	**0.0124**		
						VFAadjBMI	0.0158 (0.0066)	**0.0175**		
						VFA/SFAnoBMI	0.0229 (0.0059)	**1.19×10^{-4}**		
						VFA/SFAadjBMI	0.0199 (0.0058)	**6.54×10^{-4}**		
						SFAnoBMI	0.0131 (0.0053)	**0.0132**		
						SFAadjBMI	0.0025 (0.0037)	0.4966		

Traits were adjusted for age and sex in the additive genetic model

SNP single nucleotide polymorphism, *Chr* chromosome, *Allele* minor allele/major allele, *EAF* effect allele frequency

P values<0.05 are shown in bold

genome-wide significance in Korean populations (8842 and 7861 samples in stages 1 and 2, respectively) [34]. This locus is mapped to chromosome 12q24 in the 24th intron of the *C12orf51* and in moderate linkage disequilibrium with the rs671 at *ALDH2* in East Asian populations ($r^2 = 0.58$ in JPT and CHB). Then, two enlarged GWAS of obesity among East Asian populations were performed. The latter GWAS was conducted by Wen et al. to test the association of BMI with 2.5 million genotyped or imputed SNPs in Asian population in 2014 [21]. The significant associations of the two related SNPs in 12q24 region (rs671 at *ALDH2*, rs12229654 at *MYL2*, $r^2 = 0.58$) with BMI has been primarily identified in a population of 86,757 individuals and replicated in an independent sample of 11,233 and 23,454 individuals, respectively. The carriers of G allele (namely, highly active *ALDH2*1* allele) conferred higher BMI compared with non-carriers. There was substantial overlapping between overall obesity and central obesity and previously reported locus near *ALDH2* for WHR was not adjusted for BMI. Therefore, Wen et al. conducted a new round of meta-analyses to test the associations of WC and WHR with 2.5 million SNPs among individuals of East Asian ancestry in 2016 (n = 53,052 and 48,312 for WC and WHR, respectively) [22]. They confirmed the effects of rs671 in *ALDH2* on WC and WHR before or after adjusting for BMI. Even though WC and WHR are considered good markers for central obesity, they cannot distinguish between visceral fat and abdominal subcutaneous fat directly. The genetic study for more accurate proxy of central obesity may reveal novel variants that are not necessarily discovered when WC and WHR are used as the outcomes. The study by Wang et al. in 2016, consisted of 2958 subjects in FAt Distribution and diseasE (FADE) cohort from Chinese Han populations with refined visceral fat area (VFA) and subcutaneous fat area (SFA) imaged by MRI, explored whether *ALDH2* variants directly imposed effects on visceral fat or subcutaneous fat deposit [35]. They demonstrated that rs671 at *ALDH2* was associated with visceral fat accumulation specifically. The carriers of G allele (highly active *ALDH2*1* allele) confers more visceral fat accumulation compared with non-carriers. All of studies mentioned above indicated that *ALDH2* variants have substantial influence on obesity, especially for visceral fat accumulation.

3.3 Subgroup Analysis Stratified by Alcohol Composition

rs671 in *ALDH2* was previously demonstrated a robust association with alcohol consumption in genetic and functional studies. To evaluate the underlying effect of alcohol consumption on the association between *ALDH2* variants and obesity-related traits, the subgroup analyses were conducted but produced inconsistent results (as shown in Table 2). Two studies mentioned above by Wen et al. mainly involved a total of 6918 Chinese individuals with data of alcohol consumption available from Shanghai Genome-Wide Association Studies (SGWAS). The information about alcohol consumption was collected using a standard questionnaire. The association of rs671 with BMI was mainly observed among nondrinkers in SGWAS

Table 2 Subgroup analysis of *ALDH2* variant and obesity-related traits stratified by alcohol composition

Traits	Drinkers			Nondrinkers			*P* for interaction	Date	References
	N	*β* (SE)	*P* values	*N*	*β* (SE)	*P* values			
SGWAS cohort									
BMI	643	−0.0174 (0.0979)	0.8586	8617	0.0512 (0.0188)	**0.0065**	0.5656	2014	*Human Molecular Genetics*
WCnoBMI	643	0.0190 (0.0947)	0.8413	8616	0.0466 (0.0185)	**0.0119**	0.5950	2016	*Scientific Reports*
WCadjBMI	643	0.0327 (0.0555)	0.5568	8616	0.0084 (0.0121)	0.4843	0.7639		
WHRnoBMI	643	−0.0582 (0.0954)	0.5422	8615	−0.0003 (0.0175)	0.9861	0.0745		
WHRadjBMI	643	−0.0497 (0.0827)	0.5483	8615	−0.0195 (0.0160)	0.2218	0.0787		
FADE cohort									
BMI	1192	0.8165 (3.495)	**8.46×10^{-5}**	1696	0.1104 (−0.8466)	0.4000	**0.0071**	2016	*Scientific Reports*
WCnoBMI	1211	0.0139 (0.0028)	**9.6×10^{-7}**	1726	0.0047 (0.0019)	**0.0112**	**0.0188**		
WCadjBMI	1211	0.005 (0.0017)	**0.0024**	1726	0.0034 (0.0011)	**0.0029**	0.6301		
WHRnoBMI	1211	0.0033 (0.0016)	**0.0412**	1726	0.0004 (0.0011)	0.7063	0.2344		
WHRadjBMI	1211	0.0005 (0.0015)	0.7556	1726	0 (0.001)	0.9985	0.8903		
VFAnoBMI	1211	0.0846 (0.0154)	**5.18×10^{-8}**	1726	0.009 (0.009)	0.3197	**1.00×10^{-4}**		
VFAadjBMI	1211	0.0451 (0.0118)	**0.0001**	1726	0.0042 (0.0068)	0.5416	**0.0055**		
VFA/SFAnoBMI	1211	0.0421 (0.0119)	**0.0004**	1726	0.0058 (0.0072)	0.4216	**0.0316**		
VFA/SFAadjBMI	1211	0.0335 (0.0118)	**0.0047**	1726	0.0049 (0.0071)	0.4880	0.0973		
SFAnoBMI	1211	0.0425 (0.0104)	**4.48×10^{-5}**	1726	0.0033 (0.0066)	0.6209	**2.00×10^{-3}**		
SFAadjBMI	1211	0.0116 (0.0069)	0.0906	1726	−0.0007 (0.0048)	0.8909	0.0946		

Traits were adjusted for age and sex in the additive genetic model

P values<0.05 are shown in bold

cohort, suggesting an antagonistic effect of alcohol consumption on the *ALDH2*-BMI association. Nonetheless, WC-increasing effect or WHR-increasing effect conferred by rs671 G allele failed to be replicated among drinkers or nondrinkers separately. In FADE cohort, Wang et al. had access to individual data of alcohol consumption among a total of 2937 Chinese Han individuals. Drinkers were defined if subjects had ever consumed alcohol in their lifetime including chance drinkers (less than three times in every week) and regular drinkers (equal or more than three times in every week), whereas nondrinkers were those who never drank in their lifetime. The effects of rs671 on BMI, WC, and WHR with or without adjustment of BMI were mainly observed among drinkers. More importantly, the effect of *ALDH2* rs671 on VFA and VFA/SFA was also observed among drinkers, indicating association of rs671 with obesity-related traits mediated by alcohol consumption. Wang et al. also conducted subgroup analysis which draws a distinction between chance drinkers and regular drinkers to strengthen their findings. The results showed that the nominal associations of *ALDH2* variant with WC and VFA after adjustment of BMI were restricted to regular drinkers specifically but did not observe associations in chance drinkers. The mixed results between SGWAS and FADE study might be explained by the difference in study design. Although the definition of alcohol consumption in SGWAS and FADE study was approximately similar, the proportion of alcohol consumption was different (drinkers vs nondrinkers = 1:13 in SGWAS and 2:3 in FADE study). The possibility that BMI- or WC- or WHR-increasing effects conferred by rs671 G allele were not observed because of small sample size of drinkers in SGWAS cannot be excluded (Table 3).

3.4 Gender Difference

Generally, males have more visceral fat deposit, whereas females have more subcutaneous fat deposit before menopause. Taking into account this heterogeneity in fat distribution in both genders, the subgroup analyses in males and females were performed separately. The results showed more pronounced associations in males than in females, and there is evident heterogeneity in both gender for obesity-related traits (Table 4). Additionally, Wang et al. also tested sex difference among drinkers and nondrinkers separately. The nominal associations between the *ALDH2* variant and visceral fat accumulation were restricted to male drinkers specifically, and the effects of rs671 in *ALDH2* on VFA and SFA revealed a borderline sex-related significance among overall drinkers. Note that the male to female ratio was not balanced between drinkers and nondrinkers, that is, both of SGWAS and FADE study have more male drinkers than female drinkers. We believe that the statistical power of rs671 with central obesity-related traits in female drinkers was inadequate due to the relatively small sample size of female drinkers. The studies with comparable amount of males and females regarding to alcohol consumption to test whether alcohol consumption affect obesity or visceral fat accumulation in a sex-dependent manner are warranted.

Table 3 The analysis of rs671 and obesity-related traits in chance drinkers and regular drinkers in FADE cohort

Traits	Nondrinkers			Chance drinkers			Regular drinkers			P for interaction	Date	Reference
	N	β (SE)	P	N	β (SE)	P	N	β (SE)	P			
BMI	1696	0.1104 (−0.8466)	0.4000	625	0.8656 (0.2653)	**0.0012**	567	0.8678 (0.3533)	**0.0143**	**0.0099**	2016	*Scientific reports*
WCnoBMI	1726	0.0047 (0.0019)	**0.0112**	620	0.0127 (0.0036)	**0.0004**	565	0.0161 (0.0048)	**0.0009**	**0.0145**		
WCadjBMI	1726	0.0034 (0.0011)	**0.0029**	620	0.0036 (0.0022)	0.1071	565	0.0064 (0.0027)	**0.0174**	0.4514		
WHRnoBMI	1726	0.0004 (0.0011)	0.7063	620	0.0011 (0.0021)	0.5879	564	0.0052 (0.0027)	0.0599	0.1664		
WHRadjBMI	1726	0 (0.001)	0.9985	620	−0.0019 (0.0019)	0.3219	564	0.002 (0.0024)	0.4059	0.6961		
VFAnoBMI	1726	0.009 (0.009)	0.3197	625	0.0676 (0.0197)	**0.0007**	567	0.1056 (0.0264)	**0.0001**	**0.0001**		
VFAadjBMI	1726	0.0042 (0.0068)	0.5416	625	0.0236 (0.0146)	0.1048	567	0.0655 (0.0209)	**0.0018**	**0.0029**		
VFA/SFAnoBMI	1726	0.0058 (0.0072)	0.4216	625	0.0221 (0.0153)	0.1487	567	0.0572 (0.0202)	**0.0048**	**0.0164**		
VFA/SFAadjBMI	1726	0.0049 (0.0071)	0.4880	625	0.0102 (0.015)	0.4973	567	0.0509 (0.0201)	**0.0118**	0.0527		
SFAnoBMI	1726	0.0033 (0.0066)	0.6209	625	0.0453 (0.0133)	**0.0007**	567	0.0487 (0.0177)	**0.0062**	**0.0035**		
SFAadjBMI	1726	−0.0007 (0.0048)	0.8909	625	0.0133 (0.009)	0.1425	567	0.0149 (0.0112)	0.1860	0.1216		

Traits were adjusted for age and sex in the additive genetic model
P values<0.05 are shown in bold

Table 4 Gender difference in association of *ALDH2* variants with obesity-related traits

SNP	Nearest Gene	Allele	Traits	Males		Females		P for difference	Date	Reference
				Beta (SE)	P values	Beta (SE)	P values			
rs2074356	*ALDH2-HECTD4*	C/T	WHR	–	–	–	–	–	2009	*Nature Genetics*
rs671	*ALDH2*	G/A	BMI	–	–	–	–	–	2014	*Human Molecular Genetics*
rs12229654	*MYL2*	T/G	BMI	–	–	–	–	–		
rs671	*ALDH2*	G/A	WCnoBMI	0.1089 (0.0167)	**7.78×10^{-11}**	0.0297 (0.0106)	**0.0050**	**6.30×10^{-5}**	2016	*Scientific reports*
			WCadjBMI	0.0292 (0.0098)	**0.0029**	0.0072 (0.0064)	0.2581	0.0604	2016	
			WHRnoBMI	0.1236 (0.0183)	**1.34×10^{-11}**	−0.0017 (0.0107)	0.8727	**3.29×10^{-9}**	2016	
			WHRadjBMI	0.065 (0.0146)	**8.76×10^{-6}**	−0.0151 (0.0097)	0.1194	**4.96×10^{-6}**	2016	
rs12229654	*MYL2*	T/G	WHRnoBMI	0.1109 (0.0167)	**3.16×10^{-11}**	0.0139 (0.01)	0.1646	**6.49×10^{-7}**	2016	
			WHRadjBMI	0.0707 (0.0134)	**1.33×10^{-7}**	0.0046 (0.009)	0.6112	**4.28×10^{-5}**	2016	
			WCnoBMI	0.0969 (0.0162)	**2.45×10^{-9}**	0.0316 (0.0103)	**0.0022**	**6.85×10^{-4}**	2016	
			WCadjBMI	0.0272 (0.0085)	**0.0013**	0.0123 (0.006)	**0.0408**	0.1506	2016	
rs671	*ALDH2*	G/A	BMI	0.4053 (0.1539)	**0.0085**	0.2047 (0.1438)	0.15	0.3409	2016	*Scientific reports*
			WCnoBMI	0.01 (0.0022)	**4.05×10^{-6}**	0.0055 (0.002)	**0.0062**	0.1301	2016	

(continued)

Table 4 (continued)

SNP	Nearest Gene	Allele	Traits	Males		Females		P for difference	Date	Reference
				Beta (SE)	P values	Beta (SE)	P values			
			WCadjBMI	0.0053 (0.0012)	**7.06×10^{-6}**	0.0033 (0.0013)	**0.0104**	0.2583	2016	
			WHRnoBMI	0.0041 (0.0011)	**3.58×10^{-4}**	0.0002 (0.0012)	0.8418	**0.0166**	2016	
			WHRadjBMI	0.0026 (0.001)	**0.0087**	−0.0004 (0.0012)	0.7340	0.0548	2016	
			VFAnoBMI	0.0748 (0.0125)	**2.56×10^{-9}**	0.0057 (0.009)	0.5294	**7.25×10^{-6}**	2016	
			VFAadjBMI	0.0529 (0.0093)	**1.75×10^{-8}**	−0.0025 (0.0069)	0.7173	**1.72×10^{-6}**	2016	
			VFA/SFAnoBMI	0.0539 (0.0091)	**3.48×10^{-9}**	−0.0011 (0.0078)	0.8872	**4.46×10^{-6}**	2016	
			VFA/SFAadjBMI	0.049 (0.0089)	**4.43×10^{-8}**	−0.0027 (0.0077)	0.7241	**1.12×10^{-5}**	2016	
			SFAnoBMI	0.0209 (0.0082)	**0.0110**	0.0069 (0.0069)	0.3182	0.1914	2016	
			SFAadjBMI	0.004 (0.0051)	0.4345	0.0003 (0.0051)	0.9544	0.6080	2016	
rs2074356	*ALDH2-HECTD4*	C/T	WCnoBMI	0.0037 (0.0025)	0.1491	0.0038 (0.0023)	0.1031	0.9765	2016	
			WCadjBMI	0.0012 (0.0014)	0.3759	0.0029 (0.0015)	**0.0473**	0.4074	2016	
			WHRnoBMI	0.0023 (0.0013)	0.0877	0.0007 (0.0014)	0.6049	0.4023	2016	
			WHRadjBMI	0.0015 (0.0011)	0.1858	0.0005 (0.0013)	0.7238	0.5571	2016	

	VFAnoBMI	0.0499 (0.0147)	**6.69×10^{-4}**	0.0028 (0.0104)	0.7857	**0.0089**	2016	
	VFAadjBMI	0.0384 (0.0109)	**4.56×10^{-4}**	−0.0003 (0.0079)	0.9699	**0.0040**	2016	
	VFA/SFAnoBMI	0.0423 (0.0106)	**7.33×10^{-5}**	0.0005 (0.009)	0.9594	**0.0026**	2016	
	VFA/SFAadjBMI	0.0396 (0.0104)	**1.45×10^{-4}**	−0.0001 (0.0088)	0.9949	**0.0036**	2016	
	SFAnoBMI	0.0075 (0.0096)	0.4341	0.0025 (0.0079)	0.7561	0.6876	2016	
	SFAadjBMI	−0.0014 (0.006)	0.8180	−0.0002 (0.0059)	0.9788	0.8866	2016	

Traits were adjusted for age and sex in the additive genetic model
SNP, single nucleotide polymorphism; Chr, chromosome
P values<0.05 are shown in bold

3.5 Ethnicity

Varied ancestry populations differed in fat distribution and underlying genetic background [36, 37]. For a given amount of BMI, Asian populations seem to be prone to the accumulation of visceral fat compared to European populations [38]. An indisputable fact is that large-scale obesity GWAS that include Asian and other non-European populations are more likely to provide insight into different genetic architectures and identify evidence for specific causal genes [19, 20]. 12q24 region is polymorphic only in East Asians, and it is still unknown to what extent *ALDH2* gene contributed to the risk of visceral fat accumulation among East Asian populations exactly.

4 A Possible Model for ALDH2-Induced Obesity

The *ALDH2* gene encodes the mitochondrial ALDH2, a critical enzyme not only for ethanol oxidation during alcohol ingestion but also for several endogenous aldehydes such as propionaldehyde, butyraldehyde, and 4-hydroxykenals (4-HNE) originated from mitochondrial production of reactive oxygen species (ROS). Therefore, two plausible mechanisms have been postulated for the link between *ALDH2* variants and obesity including ethanol/acetaldehyde metabolism and endogenous bioactive aldehyde metabolism.

4.1 Proposed Mechanism One: Ethanol/Acetaldehyde Metabolism

ALDH2 encodes a functionally ALDH enzyme subunit that leads to impaired the removal of acetaldehyde, a toxic byproduct of ethanol metabolism. The A allele (also *ALDH2**2 allele), common in 30–50% of individuals of northeast Asian descent, is associated with a significantly reduced likelihood of heavy drinking and alcohol dependence due to a unpleasant symptoms like flushing, tachycardia, and nausea. The physiological and behavioral consequences of alcohol consumption serve as an intermediary process between *ALDH2* genetics and obesity. In other words, rs671 in *ALDH2* may influence the obesity and visceral fat accumulation by affecting alcohol consumption behavior, with A allele carriers having lower BMI and visceral fat depots due to lower alcohol consumption. A similar conclusion was drawn from a Mendelian randomization analysis among Korean population regarding rs671 in *ALDH2* as an instrumental variable, which indicated the marked positive effects of alcohol intake (as indexed by the absence of alcohol flushing and the *ALDH2* rs671 GG genotype) on blood pressure [39].

Recent evidence indicated that excess drinking was consistently associated with weight gain or increased waist circumference, whereas light-to-moderate alcohol consumption is not linked to adiposity gain [40–42]. Further, Molenaar et al. [43] reported that intake of large amounts of alcohol was associated with decrease of subcutaneous adiposity in females and increase of visceral adiposity in males from Framingham Offspring Study. A common trend appears to be that it is multifactorial and involves cross talk among various organs and tissues.

In food, the energy content is derived from macronutrients (carbohydrate, fat, protein, and alcohol). Both of carbohydrate and protein provide 4 kcal per gram and fat provides 9 kcal per gram. Alcohol is a calorically dense substance and produces 7.1 kcal (29 kJ) per gram [44], which should theoretically play a critical role in energy balance. The findings about the effects of alcohol-derived energy on body mass and fat deposit are debatable. A line of evidence indicates that alcohol-derived calorie consumption seems to supplement food-derived energy [45, 46], and individuals with excessive drinking appear to increase adiposity indices among varied populations [47–50]. A diet recall study in 951 healthy males from Koreans, which recorded the dietary intake of energy from food and alcohol, showed that total energy intake increased with higher alcohol consumption and further observed that there was an increase in visceral fat accumulation with either decrease or no change in subcutaneous fat accumulation [51]. Another study, however, found that chronic and moderate alcohol intake was likely to lead to a decrease in macronutrients intake to compensate for ethanol calories [52]. A certain number of studies have examined the short-term effect of alcohol consumption on appetite control and feeding behavior. In these studies, alcohol may amplify individuals' perception of appetite in response to food stimuli but fail to produce sufficient signals on satiety or enhance the rewarding effects [53–55]. Besides, several neurotransmitters including γ-aminobutyric acid (GABA), opioid and dopaminergic system were considered to be vital for motivational effect of alcohol on stimulation of appetite [56, 57]. Genomic-based evidence showed that compared to individuals with the GG genotype (*ALDH2*1/*1* homozygotes), those with the inactive A allele (*ALDH2*2*) reported greater negative alcohol expectancies, and lower risk of alcohol abuse, indicating that differences in alcohol metabolism were reported to influence how drinking events are experienced, interpreted, and stored in memory in central nervous system [58].

Abundance of data showed that higher amounts of daily alcohol intake were positively associated with visceral adiposity [43, 59, 60]. The correlation between alcohol intake and fat distribution was likely mediated by plasma androgens at least in part or fatty liver, which can result in hepatic insulin resistance and subsequent weight gain. Several studies, however, have been rather inconsistent, reporting no association between alcohol consumption and visceral fat [61, 62]. Genomic-based evidence indicated that *ALDH2* variants strongly correlated with obesity, especially for visceral fat accumulation. Further studies are required to validate the association and get understanding of the mechanism process of ALDH2 which manifested as visceral adiposity.

Moreover, increasing studies showed that excess alcohol consumption were often associated with chronic systemic inflammation status and high circulating proinflammatory cytokine levels [63–65] as well as high circulating cortisol levels [66, 67]. Alcohol intake may enhance cortisol secretion which changed the pattern of fat distribution, together with an increase in abdominal and hepatic fat deposition and subcutaneous adiposity lipolysis [66].

Obesity is a combination of genetic and environmental factors. These factors may act independently or they may interact with each other. Gene-environment interaction, in a statistical sense, refers to a situation in which the impacts of genes depend on the environment or the impacts of the environment depend on genotype [68]. For example, a study found that *GNB3* variation interacts with physical activity to influence obesity. They reported that carriers of 825 T allele in physical active group had a 20% lower prevalence of obesity for each additional T allele, while those with the same genotype who were not physically active had a 23% greater prevalence of obesity [69]. The integration of gene-environment information is crucial to move genomic discoveries in obesity to actual behavioral interventions or medications that reduce the burden of obesity. Previous genomic-based evidence indicated the association of *ALDH2* variants with obesity-related indices, which were mediated with alcohol consumption. However, the knowledge on how *ALDH2* and environment interact at a biological level is crucial in fully understanding the processes of obesity or visceral fat accumulation but remains unclear currently. Research on the advance of a wide range of biological responses (e.g., energy intake, appetite control, systemic inflammation, or some hormones) after alcohol consumption in the internal environment among individuals with certain genotype is needed.

4.2 Proposed Mechanism Two: Endogenous Bioactive Aldehyde Metabolism

In the body, several degradation reactions are known to form endogenous acetaldehyde during the oxidative stress, many of which are highly reactive and toxic. Apart from alcohol metabolism, ALDH2 is also responsible for oxidizing several bioactive aldehydes (i.e., propionaldehyde, butyraldehyde, and 4-HNE). It is suggested that ALDH2 could protect against oxidative stress-related diseases such as atherosclerosis, tumors, diabetes, and acute lung injury and pulmonary arterial hypertension [70–72]. Recent evidence indicated that reactive oxygen species (ROS) balance was required for the physiology adipocyte function and differentiation. Yu et al. reported that ALDH2 overexpression or ALDH2 agonist Alda1 was correlated with adipocyte differentiation, mediated by signaling pathways downstream of peroxisome proliferator-activated receptor (PPAR)-γ [72]. As oxidative stress is consolidated in obesity complications such as cardiomyopathy, Wang et al. reported that ALDH2 can help preserve high-fat diet-induced obesity cardiomyopathy through a

mechanism related to modulation of autophagy and SUV39H-Sirt1-dependent PGC-1α deacetylation [73].

5 Ways Ahead and Conclusions

Great advance has been made through GWAS in different ethnic groups for the discovery the susceptibility of obesity. Findings of this research in large-scale population-based studies have proven significant to advancing our knowledge of the pathways by which obesity development is modulated. Currently, evidence on quantifying the role of gene-environment interactions in the development of obesity, which are crucial for clinical or public health practice, is still lacking. Along this review, we illustrated the available evidence on *ALDH2* variants and obesity and then proposed a model by which the physiological and behavioral consequences of alcohol consumption are considered to be an intermediary process between *ALDH2* genetics and obesity. This integration of *ALDH2* variants and environment or personal behavior is of great value: (1) shedding new light on the role of aldehyde dehydrogenases in biology process in humans, (2) improving the integration of currently uncertain data on alcohol consumption in etiology of obesity, and (3) regarded as an important way to understand the functional diversity of the numerous genetic polymorphisms for obesity and any other serious, chronic pathologies and ultimately to improve population health.

However, to explore the interpretation of genetic findings to environmental factors for obesity or fat distribution is currently in the early stage, and much of that should be validated. First, to obtain the better assessments of gene-environment interactions, alcohol type as well as consumption pattern including frequency and amount of alcohol intake should be taken into account in quantitative models. Measurement of environmental factors including behavioral and lifestyle factors appears to be less certain and complete rather than measurement of the genomics in epidemiological studies. Therefore, the advances in genomics on intervention and management of obesity will depend on the reliability of evidence obtained from epidemiological studies. Second, whether alcohol-derived metabolites per se or other endogenous reactive dehydrates play a key role in regulation of obesity should be studied since the cytoprotection of ALDH2 is considered to be a prominent function for a variety of human diseases. Another concern is that the usefulness of *ALDH2*-variants findings should be determined through longitudinal studies or intervention studies. Such longitudinal studies in which *ALDH2* variants could be of predictive value or serve as markers to identify individuals who are at high risk of obesity are warranted. Additional research on behavioral interventions targeted to subgroups with varied genotypes is needed to understand behavioral responses to genetic information. For instance, researchers might as well examine whether health guidance based on genetic testing would be more beneficial in framing behavior of certain genotype subgroup.

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