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Original Article

Genetic variants of *ALOXs* genes in polyunsaturated fatty acid/arachidonic acid metabolism associated with type-2 diabetes development

Jim Jinn-Chyuan Sheu[1,3,4,5*], Ying-Ju Lin[1,3*], Cherry Yin-Yi Chang[2], Shih-Yin Chen[1,3], Wen-Ling Liao[1,4], Jai-Sing Yang[1], Ming-Tsung Lai[6], Chih-Mei Chen[1], Chun-Cheng Tseng[4], Tritium Hwang[4], Ping-Ho Chen[7], Fuu-Jen Tsai[1,3]

[1]Human Genetic Center, [2]Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan; [3]School of Chinese Medicine, China Medical University, Taichung, Taiwan; [4]Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan; [5]Department of Health and Nutrition Biotechnology, Asia University, Taichung, Taiwan; [6]Department of Pathology, Taichung Hospital, Ministry of Health and Welfare, Taichung, Taiwan; [7]School of Dentistry, Kaohsiung Medical University, Kaohsiung, Taiwan. [*]Equal contributors.

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Abstract: Poly-unsaturated fatty acids (PUFAs)/arachidonic acids (AAs) and their derived eicosanoids play potent roles in triggering inflammation during obesity and diabetes development. Recent studies have indicated functional roles of *ALOX5*, *ALOX12*, *ALOX12B*, and *ALOX15* in the development of insulin resistance and islet β-cell dysfunction. However, the impact of their genetic variants on type 2 diabetes (T2D) development in Asian patients remains unclear. In this study, 1,682 healthy controls and 788 patients with T2D were enrolled for genotyping those four *ALOX* genes by the *TaqMan* method. A total of eight Han Chinese-specific SNPs (two SNps for each gene) were selected for this study. Of the SNPs tested, genetic variations in *ALOX12* (rs312462) and *ALOX12B* (rs.4792199 and rs.4792216) were found to be significantly associated with T2D development. Multivariable regression analysis further revealed the genetic variation at rs.4792199 as a potential independent marker as age (older than 52) or BMI (higher than 25) for T2D prognosis. When T2D patients were stratified according to age and BMI, SNPs in both *ALOX12* (rs312462) and *ALOX12B* (rs.4792199 and rs.4792216) showed significant impact on T2D development. The present study confirms the involvement of *ALOX12* and *ALOX12B* genetic variants in conferring susceptibility to T2D development, possibly though alterations in PUFA/AA metabolism.

Keywords: Type 2 diabetes (T2D), lipoxygenases (ALOXs), polyunsaturated fatty acid (PUFA), arachidonic acid (AA), eicosanoids

Introduction

Chronic inflammation is a clinical feature associated with type 2 diabetes (T2D) and its related complications, especially in obese patients. Emerging evidence has supported the point of view that dysregulated lipid metabolism in adipose tissue is the key step in altering cellular cross-talk between adipocytes and surrounding/infiltrative immune cells, like macrophages, resulting in pro-inflammatory cytokine secretion [1, 2]. Accumulation of bioactive lipid species, including diacylglyerol, ceramides, and fatty acyl-coenzyme A, can also impair insulin signaling by inactivation of insulin receptors and their substrates, leading to insulin resistance [3, 4]. Since the inter-relationship between accumulation of lipid toxicity and chronic inflammation is bi-directional [5], a greater rate of fatty acid breakdown and uptake in diabetes patients has been suggested as an unfavorable marker for detrimental outcomes. Enzyme regulation involved in lipid metabolic programming, therefore, plays important roles in T2D development.

Metabolism of polyunsaturated fatty acid (PUFA) and primarily arachidonic acid (AA) has grabbed attention in T2D studies in recent years due to the signaling involvement in immune/inflammatory response [6, 7]. AAs are components of phospholipids in cell mem-

Table 1. General characteristics of T2D patients and non-T2D controls[a]

Characteristics	T2D N = 788 N (%)	Non-T2D N = 1682 N (%)	*p*-value[b]
Age			*< 0.0001***
< 52 years old	187 (23.73%)	1037 (61.65%)	
≥ 52 years old	601 (76.27%)	645 (38.35%)	
Gender			*0.0029***
Male	445 (56.47%)	842 (50.06%)	
Female	343 (43.53%)	840 (49.94%)	
BMI[c]			*< 0.0001****
< 25	284 (36.04%)	933 (55.47%)	
≥ 25	504 (63.96%)	749 (44.53%)	
WHR ratio[d]			*< 0.0001****
< 0.89	206 (26.14)	1053 (62.60)	
≥ 0.89	582 (73.86)	629 (37.40)	

[a]Abbreviations: T2D, type 2 diabetes; BMI, body mass index; WHR ratio, waist-to-hip ratio. [b]*p*-values were calculated by Chi-squared test. Statistical significance expressed as *bold italic* with a *p*-value < 0.05. Statistical significance (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$). [c]BMI was calculated as ((height (cm)/[weight (kg)]^2). [d]WHR was calculated as (waist (cm)/hip (cm)).

branes, especially abundant in the brain, muscles, and liver, the three major energy-sinks for glucose and fatty acids in human body. Their well-known metabolites are eicosanoids, functioning as a complex family of lipid mediators or intracellular second messengers to regulate a wide variety of physiological and pathological processes [8, 9]. More importantly, these derivatives have been reported to affect glucose-stimulated insulin secretion from pancreatic β-cells [10, 11].

At least three types of enzymes have been found to participate in the metabolism of PUFAs and AAs, lipoxygenases (ALOXs), cyclooxygenases (COXs), and cytochrome p450 epoxygenases (CYP450s) [9, 10]. The initial products during PUFA/AA conversion are hydroperoxyeicosatetraenoic acids (HpETEs) and hydroxyeicosatetraenoic acids (HETEs) through oxygenation reactions predominantly catalyzed by various ALOXs [9]. Currently, the well-studied ALOXs include *ALOX5*, *ALOX12*, *ALOX12B*, and *ALOX15*. They promote PUFA/AA oxidation at 5-, 12-, 12R-, and 15- positions, respectively. These ALOXs are expressed in many tissues and inflammatory cells, playing roles in inflammation response and associated disorders, including T2D. For example, *ALOX5* has been found as a mediator for inflammation-induced vascular complications [12, 13] and critical for the development of T2D-ratinopathy [14]. *ALOX12* and *ALOX15* are functionally similar in AA metabolism and activate to trigger adipose tissue inflammation [15, 16]. In particular, *ALOX12* upregulation triggered by adipokines or hyperglycemia has been identified as a causal factor for islet β-cell dysfunction in T2D [17]. Functioning as stereochemistry to *ALOX12*, *ALOX12B* converts AA to 12R-HpETE or 12R-HETE, potent pro-inflammatory mediators in the human body [18].

The above studies provide strong evidence to support the involvement of these common ALOXs in inflammatory response and T2D development. Inhibitors targeting ALOXs have been under development or clinical trials that aim to reduce insulin resistance and obesity-related comorbid conditions [15-17, 19]. However, their genetic impact on Asian patients with T2D remains largely unknown. This study aimed to explore the genetic association of Han Chinese-specific SNPs in those common ALOX genes. The clinical impact of their genetic variants was studied and discussed.

Materials and methods

Study population

The study cohort consisted of 788 patients diagnosed with T2D at the China Medical University Hospital in Taiwan, between 2009-2016. The control group consisted of 1,682 individuals that received regular physiological checks. They were proven to be healthy based on examinations conducted. T2D-related clinical characteristics of each study subject were verified by clinical reports. General characteristics of T2D patients and non-T2D controls are shown in **Table 1**. This study was approved by the Institutional Review Board of the China

Table 2. Allele distributions of SNPs in PUFA/AA lipoxygenase genes in Taiwanese patients with T2D and controls[a]

Gene	SNP	MAF		OR	95% CI	*p*-value[b]
		Patients (n = 788)	Controls (n = 1682)			
ALOX5	rs1864414	37.37%	35.26%	1.10	0.97-1.24	0.15
	rs10751383	29.51%	31.15%	0.92	0.81-1.05	0.24
ALOX12	rs311743	48.60%	49.91%	0.92	0.81-1.05	0.24
	rs312462	16.50%	15.01%	1.13	0.96-1.33	0.14
ALOX12B	rs4792199	30.14%	34.99%	0.80	0.70-0.91	***0.0008****
	rs4792216	42.77%	38.88%	1.17	1.04-1.33	***0.0094****
ALOX15	rs1038121	7.74%	8.29%	0.93	0.74-1.16	0.51
	rs4790689	20.62%	20.42%	1.01	0.87-1.17	0.86

[a]Abbreviations: SNP, single nucleotide polymorphism; PUFA, poly-unsaturated fatty acid; AA: arachidonic acid; T2D: type-2 diabetes; MAF, minor allele frequency; OR, odds ratio of minor alleles with reference to major alleles; 95% CI, 95% confidence interval; ALOX5, arachidonate 5-lipoxygenase; ALOX12, arachidonate 12-lipoxygenase; ALOX12B, arachidonate 12-lipoxygenase, 12R type; ALOX15, arachidonate 15-lipoxygenase. [b]*p*-values were calculated by Chi-squared test. Statistical significance expressed as ***bold italic*** with a *p*-value < 0.05. Statistical significance (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$).

Medical University Hospital (IRB-CMUH), with informed consent provided by each participant.

Genotyping of selected SNPs in ALOX genes

Peripheral blood was collected from individual at clinics and genomic DNA was extracted from the buffy coat, according to standard protocol (Genomic DNA kit; Qiagen, Valencia, CA, USA). DNA fragments containing the SNP sites were amplified by PCR using the TaqMan SNP genotyping assay system (Applied Biosystems Inc. Carlsbad, CA, USA) with probe IDs listed in Table S1. A positive signal was generated when a perfect match formed between the probe and the tested DNA fragment. By reading defined fluorescence signals of PCR products, genetic variations in study cohorts were monitored and recorded.

Statistical analyses and clinical impact

Distributions of allelic and genotypic frequency in patients, as well as in controls, were analyzed and compared by Chi-squared test using SPSS software (version 10.0, SPSS Inc. Chicago, IL, USA). Data are expressed as percentages of the total number of alleles and genotypes. Odds ratios (ORs) were calculated for allelic and genotypic frequencies with 95% confidence intervals (95% CIs), using the wild type allele as the reference. Clinical characteristics associated with a specific SNP were compared between groups using two independent t-tests. A *p* value less than 0.05 is considered statistically significant. Statistical significance, *: *p* value < 0.05, **: *p* value < 0.01, ***: *p* value < 0.001.

Results

T2D risk association analysis of Han Chinese-specific SNPs in ALOX genes

To study whether genetic variations in genes involved in PUFA/AA metabolism predispose to T2D development, Han Chinese-specific SNPs were selected for genotyping in *ALOX5*, *ALOX12*, *ALOX12B*, and *ALOX15* genes (Table S1) [20, 21]. Allelic type analyses indicated the involvement of *ALOX12B* genetic variants in T2D development. The SNP at rs4792199 showed a protective role ($P = 7.6 \times 10^{-4}$; OR: 0.80; 95% CI: 0.70-0.91) while the SNP at rs4792216 exhibited a promotive role ($P = 9.4 \times 10^{-3}$; OR: 1.17; 95% CI: 1.04-1.33) on T2D development (**Table 2**). Genotypic analyses confirmed significant association of genotype distributions of rs312462 (in *ALOX12*) ($P = 0.030$), rs4792199 (*ALOX12B*) ($P = 0.029$), and rs4792216 (*ALOX12B*) ($P = 0.029$) with T2D development.

Genetic impact of SNPs in ALOX genes on T2D development

With protective potential (**Table 2**), the SNP at rs4792216 (*ALOX12B*) showed a dominant effect on genotype distribution, indicating that people with TT or CT genotypes were at a lower risk for T2D, compared to people with CC genotype ($P = 11.3 \times 10^{-4}$; OR: 0.80; 95% CI: 0.68-0.95). Such protective effects can be stronger in a recessive model with higher statistical significance ($P = 2.2 \times 10^{-4}$; OR: 0.64; 95% CI: 0.49-0.86). Although genetic variations at both rs312462 (*ALOX12*) and rs4792216 (*ALOX12B*) revealed T2D-promotive effects by genotype analyses, their genetic impact on T2D develop-

Table 3. Genotype distributions of genetic variants in the ALOX gene family between T2D and control groups

Gene	SNP genotype	T2D N = 788 N (%)	Non-T2D N = 1682 N (%)	*p*-value	Dominant model Recessive model	Odds ratio (95% CI)	*p*-value
ALOX5	rs1864414			0.144	(GG+TG) v.s. TT	*1.20 (1.00-1.45)*	*0.0490**
	TT	232 (29.4)	562 (33.4)		GG v.s. (TG+TT)	1.07 (0.70-1.14)	0.75
	TG	523 (66.4)	1054 (62.7)				
	GG	33 (4.2)	66 (3.9)				
	rs10751383			0.449	(AA+CA) v.s. CC	0.90 (0.76-1.06)	0.21
	CC	393 (49.9)	793 (47.1)		AA v.s. (CA+CC)	0.93 (0.70-1.25)	0.64
	CA	325 (41.2)	730 (43.4)				
	AA	70 (8.9)	159 (9.5)				
ALOX12	rs311743			0.217	(GG+TG) v.s. TT	1.02 (0.84-1.23)	0.86
	TT	204 (25.9)	441 (26.2)		GG v.s. (TG+TT)	0.85 (0.70-1.04)	0.12
	TG	402 (51)	803 (47.7)				
	GG	182 (23.1)	438 (26)				
	rs312462			*0.030**	(AA+GA) v.s. GG	1.06 (0.88-1.28)	0.54
	GG	557 (70.7)	1209 (71.9)		AA v.s. (GA+GG)	*1.97 (1.18-3.28)*	*0.0079***
	GA	202 (25.6)	441 (26.2)				
	AA	29 (3.7)	32 (1.9)				
ALOX12B	rs4792199			*0.029**	(TT+CT) v.s. CC	*0.80 (0.68-0.95)*	*0.0113**
	CC	383 (48.6)	726 (43.2)		TT v.s. (CT+CC)	*0.64 (0.49-0.86)*	*0.0022***
	CT	335 (42.5)	735 (43.7)				
	TT	70 (8.9)	221 (13.1)				
	rs4792216			*0.029**	(TT+CT) v.s. CC	1.18 (0.99-1.41)	0.0621
	CC	266 (33.8)	633 (37.6)		TT v.s. (CT+CC)	*1.31 (1.05-1.64)*	*0.0155**
	CT	370 (47)	790 (47)				
	TT	152 (19.3)	259 (15.4)				
ALOX15	rs1038121			0.263	(CC+TC) v.s. TT	0.90 (0.76-1.06)	0.21
	TT	667 (84.6)	1413 (84)		CC v.s. (TC+TT)	NA	NA
	TC	120 (15.2)	259 (15.4)				
	CC	1 (0.1)	10 (0.6)				
	rs4790689			0.859	(AA+CA) v.s. CC	1.00 (0.84-1.19)	0.99
	CC	495 (62.8)	1056 (62.8)		AA v.s. (CA+CC)	1.12 (0.73-1.74)	0.60
	CA	261 (33.1)	565 (33.6)				
	AA	32 (4.1)	61 (3.6)				

[a]Abbreviations: T2D, type 2 diabetes; OR, odds ratio; CI, confidence interval; ALOX5, arachidonate 5-lipoxygenase; ALOX12, arachidonate 12-lipoxygenase; ALOX12B, arachidonate 12-lipoxygenase, 12R type; ALOX15, arachidonate 15-lipoxygenase.
[b]*p*-values were calculated by Chi-squared test. Statistical significance expressed as *bold italic* with a *p*-value < 0.05. Statistical significance (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$).

ment was recessive. A allele of the SNP at rs312462 (*ALOX12*) ($P = 7.9 \times 10^{-3}$; OR: 1.97; 95% CI: 1.18-3.28) and T allele of the SNP at rs4792216 (*ALOX12B*) ($P = 0.016$, OR: 1.31; 95% CI: 1.05-1.64) recessively increased T2D susceptibility (**Table 3**). Present data revealed the association of genetic variations in *ALOX12* and *ALOX12B* with T2D development. Genotype analyses for SNPs in *ALOX5* (rs1864414 and rs10751383) and *ALOX15* (rs1038121 and rs4790689) showed no association with T2D development. However, genetic variations at rs1864414 (*ALOX5*) did show weakly promotive effects on T2D development in a dominant model ($P = 0.049$, OR: 1.20; 95% CI: 1.00-1.45) (**Table 3**).

Table 4. Multivariable regression analysis on the risk factors of T2D[a]

Risk factors	β coefficients	SE	T	*p*-value[b]
Age	0.016	0.001	23.29	*< 0.001****
Gender (Male/Female)	0.017	0.017	1.04	0.298
BMI	0.021	0.002	9.63	*< 0.001****
WHR	0.045	0.031	1.44	0.151
rs4792199 (CC+TC/TT)	0.061	0.026	2.37	*0.018**
rs4792216 (CC+TC/TT)	-0.036	0.022	-1.61	0.107

[a]Abbreviations: T2D, type 2 diabetes; SE, standard error; T, the t statistic; BMI, body mass index; WHR ratio, waist-to-hip ratio. [b]*p*-values were calculated by Chi-squared test. Statistical significance expressed as *bold italic* with a *p*-value < 0.05. Statistical significance (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$).

Genetic variations in ALOX12 and ALOX12B genes and their correlations with other risk factors

To examine whether T2D-related SNPs could serve as independent markers, multivariate regression analyses were performed to study the impact of genetic variations in *ALOX12B* (rs4792199 and rs4792216) on T2D susceptibility with other T2D-associated risk factors. As shown in **Table 4**, significant clinical factors associating with T2D development in the Taiwanese cohort were older age (≥ 52 yr; $P < 0.001$) and higher BMI (≥ 25; $P < 0.001$). As with these two factors, a dominant model of the wild type C allele at rs4792199 (*ALOX12B*) showed genotypic predisposition ($P = 0.018$) to T2D development after multivariable regression with other related risk factors (**Table 4**). Furthermore, stratification of T2D patients, according to age and BMI, identified dominant genotypic effects of the SNP at rs312462 (*ALOX12*) ($P = 0.032$; OR: 1.55; 95% CI: 1.04-2.01) and wild type C allele at rs4792216 (*ALOX12B*) ($P = 0.045$; OR: 0.64; 95% CI: 0.41-0.99) for patients with ages older than 52 and BMIs less than 25 (**Table 5**). This study also identified dominant genotypic effects of the wild type C alleles at both rs4792199 (*ALOX12*) ($P = 0.036$; OR: 1.69; 95% CI: 1.04-2.75) and rs4792216 (*ALOX12B*) ($P = 0.042$, OR: 0.66; 95% CI: 0.44-0.98) for patients with ages older than 52 and BMIs higher than 25 (**Table 5**). Present data confirmed the impact of *ALOX12* and *ALOX12B* genetic risk factors on T2D risk when patients were stratified according to age and BMI.

Discussion

T2D is a metabolic and chronic disorder frequently complicated with cardiovascular disease, strokes, diabetic nephropathy, neuropathy, and retinopathy [22, 23]. Epidemiological studies have also revealed higher incidence rates of certain types of cancers in Asian T2D patients [24, 25]. Molecular mechanisms involved in such pathogenesis have been found to be related to chronic inflammation [1, 2, 26, 27]. Clinical investigation has confirmed that circulating inflammatory markers, like eicosanoids, are increased during T2D development and their levels appear to predict onset and progression of diabetic complications [8, 28]. Therapeutic agents against inflammatory and immune processes are, therefore, considered as potential useful interventions that may benefit T2D patients [26, 27]. ALOXs are dioxygenases frequently expressed in immune, epithelial, and tumor cells, participating in the biosynthesis of pro- and anti-inflammatory lipid mediators, including eicosanoids [19, 29, 30]. Thus, ALOXs have been implicated in a variety of physiological functions, including inflammation, skin disorders, and tumorigenesis. The present study confirmed that SNPs in *ALOX12* (rs312462) and *ALOX12B* (rs4792199 and rs4792216) genes determine genetic susceptibility to T2D development. In addition to their biochemical influence on inflammatory processes, this study provides evidence revealing the genetic impact of dioxygenases on this devastating disorder.

ALOX12 is expressed in metabolically active tissues, suggested to play a pro-inflammatory role during PUFA/AA metabolism [17, 30]. The major eicosanoid produced by *ALOX12* is 12S-HETE, functioning as a chemotaxis of inflammatory cells, like neutrophils monocytes and macrophages, leading to local inflammation [31, 32]. When upregulated in islet cells by high blood glucose or fatty acids, 12S-HETE has been found to generate oxidative stress and ER shock through activation of Nox-1 and ROS, further causing β-cell dysfunction and cell death [17]. Interestingly, functional knockdown

Table 5. Effects of ALOX12 and ALOX12B genetic risk factors on T2D risk when stratified according to age and BMI[a]

Gene	SNP	Genotype stratified by age and BMI	OR	95% CI	*p*-value[b]
ALOX12	rs312462	AA+AG vs GG, Age < 52, BMI < 25	1.21	0.63-2.32	0.57
		AA+AG vs GG, Age < 52, BMI ≥ 25	1.12	0.71-1.78	0.63
		AA+AG vs GG, Age ≥ 52, BMI < 25	1.55	1.04-2.01	*0.032**
		AA+AG vs GG, Age ≥ 52, BMI ≥ 25	0.80	0.57-1.13	0.21
ALOX12B	rs4792199	CC+TC vs TT, Age < 52, BMI < 25	3.49	0.83-14.70	0.09
		CC+TC vs TT, Age < 52, BMI ≥ 25	1.21	0.66-2.22	0.53
		CC+TC vs TT, Age ≥ 52, BMI < 25	1.65	0.95-2.59	0.07
		CC+TC vs TT, Age ≥ 52, BMI ≥ 25	1.69	1.04-2.75	*0.036**
	rs4792216	CC+TC vs TT, Age < 52, BMI < 25	1.12	0.51-2.46	0.78
		CC+TC vs TT, Age < 52, BMI ≥ 25	1.27	0.73-2.22	0.40
		CC+TC vs TT, Age ≥ 52, BMI < 25	0.64	0.41-0.99	*0.045**
		CC+TC vs TT, Age ≥ 52, BMI ≥ 25	0.66	0.44-0.98	*0.042**

[a]Abbreviations: T2D, type 2 diabetes; BMI, body mass index; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; ALOX12, arachidonate 12-lipoxygenase; ALOX12B, arachidonate 12-lipoxygenase, 12R type. [b]*p*-values were calculated by Chi-squared test. Statistical significance expressed as *bold italic* with a *p*-value < 0.05. Statistical significance (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$).

of *ALOX12* in mice by genetic manipulation can improve insulin sensitivity, β-cell function, and glucose tolerance, with reduced macrophage infiltration in adipose tissues and proinflammatory cytokine levels when mice are treated with a high-fat diet [33, 34]. A recent study has discovered an SNP (rs2073438) in *ALOX12* genes that significantly associates with total and percentage fat mass of obese men, compared to non-obese young Chinese men [35]. These studies, in combination with present findings, suggest potent roles of *ALOX12* in energy metabolism and cellular inflammation in the setting of diabetes development.

The stereoisomer of 12S-HETE is 12R-HETE. It is produced by another dioxygenase, *ALOX12B*. Although *ALOX12B* is frequently associated with skin development and psoriasis [36, 37], emerging evidence has supported that 12R-HETE stimulates neutrophil chemotaxis [38]. Especially, 12R-HETE can be detected in microvessel epithelial cells [39], suggesting its possible roles in T2D-associated microvascular inflammation and related complications. One important finding is that patients with psoriasis have an increased prevalence and incidence of diabetes [40, 41]. Epidemiological studies have also indicated the link between psoriasis and hypertension [42], obesity [43], non-alcoholic fatty liver [44], and atherosclerosis [45]. These data support the possible involvement of *ALOX12B* genetic variations in T2D development, as found in this present study.

The current study showed weak association of genetic variations in *ALOX5* (rs1864414) and no association in *ALOX15* (rs1038121 and rs4790689) with T2D development. To the best of our knowledge, no T2D-associated SNP has been reported in *ALOX15* genes to date. However, some studies have revealed the genetic impact of *ALOX5* on myocardial infarction [46] and T2D-associated atherosclerosis [47]. Clinical studies have also indicated that components in *ALOX5* pathways are highly expressed in arterial walls in patients with atherosclerosis of the carotid and coronary arteries [48]. Notably, *ALOX15* was recently found to be either pro- or anti-inflammatory during the development of atherosclerosis, depending on the presence of lipoxins in the arterial walls [49]. Thus, more study is needed to further address its roles in T2D development.

Results from the present study suggest that PUFA/AA lipoxygenase genes *ALOX12* and *ALOX12B* play crucial roles in T2D development, both at protein and genetic levels. Genetic variations in these two genes may also have pleiotropic effects on multiple components associated T2D, such as age and BMI.

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All peripheral blood samples were obtained after written documentation of informed consent from each patient or legal representative. Copies of consent have been collected for archiving by the Human Genetic Center, China Medical University Hospital, Taichung, Taiwan. All the study subjects involved in this study gave their consent to publish the data obtained.

Disclosure of conflict of interest

None.

Abbreviations

T2D, type 2 diabetes; PUFA, poly-unsaturated fatty acid; AA, arachidonic acid; SNP, single nucleotide polymorphism; ALOX5, arachidonate 5-lipoxygenase; ALOX12, arachidonate 12-lipoxygenase; ALOX12B, arachidonate 12-lipoxygenase, 12R type; ALOX15, arachidonate 15-lipoxygenase.

Address correspondence to: Jim Jinn-Chyuan Sheu, Institute of Biomedical Sciences, National Sun Yat-sen University, IR4013, No. 70, Lianhai Road, Gushan District, Kaohsiung 80424, Taiwan. Tel: +886-7-5252000 Ext. 5811; Fax: +886-7-5250197; E-mail: jimsheu@mail.nsysu.edu.tw; Fuu-Jen Tsai, Human Genetic Center, China Medical University Hospital, No. 2, Yude Road, North District, Taichung 40447, Taiwan. Tel: +886-4-22053366 Ext. 1015; Fax: +886-4-22033295; E-mail: d0704@mail.cmuh.org.tw

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Table S1. Information of probe TaqMan IDs used for genotyping of *ALOX* genes[a]

Gene	SNP	Probe ID
ALOX5	rs1864414	C___2046455_20
	rs10751383	C___2046351_10
ALOX12	rs311743	C___749093_10
	rs312462	C___749063_20
ALOX12B	rs4792199	C___9277039_10
	rs4792216	C___9277006_10
ALOX15	rs1038121	C___8718659_10
	rs4790689	C___29881702_10

[a]Abbreviations: SNP, single nucleotide polymorphism; ALOX5, arachidonate 5-lipoxygenase; ALOX12, arachidonate 12-lipoxygenase; ALOX12B, arachidonate 12-lipoxygenase, 12R type; ALOX15, arachidonate 15-lipoxygenase.