PPARD rs7770619 polymorphism in a Korean population: association with plasma malondialdehyde and impaired fasting glucose or newly diagnosed type 2 diabetes

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감사의 글

2009년에 혼자서 한국, 이 낯선 땅에 들어왔고 연세대학교에서 길고도 짧은 4년 학부, 2년의 석사 생활이 끝나가면서 이 글을 통해 그동안 저를 학업과 생활에 도와주고 격려해 주신 분께 감사한 마음을 전해드리고 싶습니다.

먼저 학부 시절부터 저를 잘 이끌어주시고 부족한 저에게 소중한 기회를 주어 교수님 연구실에서 계속 공부할 수 있게 해주신 이종호 교수님께 깊은 감사한 마음을 전해드리고 싶습니다. 그동안 수많은 어려움을 겪었지만, 공부와 생활에 계속 도와주신 이종호 교수님, 진심으로 감사드립니다. 곧 졸업해서 연구실 떠나지만, 어느 곳에 가더라도 교수님의 은혜를 잊지 않겠습니다. 교수님의 제자로서 앞으로 부끄럽지 않게 늘 노력하겠습니다.

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짧았던 2년간의 연구실 생활이었지만, 평생 잊지 못할 아름다운 추억을 함께 만들어주신 연구실 식구들에게도 감사한 마음을 전해 드리고 싶습니다. 학부시절, 멋진 강의를 통해 저를 이 길로 이끌어주시고, 연구실을 위해 묵묵히 애써주신

채지숙 교수님, 연구실의 초석이라고 할 수 있으며 세심하신 5층 김민주 박사님, 김민경 박사님, 유혜진 박사님, 그리고 노화과학협동과정의 모든 업무를 관리하여 수고가 많으신 구정임 누나께 감사를 드립니다. 바쁜 박사 업무를 하면서도 저에게 좋은 조언을 아끼지 않으시고 도와주신 아영 누나, 지숙 누나, 인원수가 제일 적은 3학기이지만 연구실에서 중요한 역할을 하는 민식 형, 주연이, 에너지 넘치는 2학기 가현 누나, 여민이, 민정이, 소현이, 지윤이, 효은이 그리고 인혜, 들어온 지 얼마 안 됐지만, 이제 연구실 업무를 능숙히 할 줄 아는 1학기 사랑이, 정민이, 예진이, 춘이, 나희, 민정이, 화나. 여러분 덕분에 연구실 업무에 트이게 되었고 이렇게 결실을 맺게 되었습니다. 감사합니다.

그리고 제일 소중한 우리 동기들! 늘 명랑한 웃음소리와 함께 등장하는, 똑똑하고 매사 꼼꼼한 자영이, 활발하면서 귀엽고 어딜 가더라도 큰 가방을 매는 바쁜 예리, 경상도 미인이면서 애교도 많고, 활발하지만 일할 때는 빈틈없이 세심하고 꼼꼼한 반전 모습을 보여주는 멋있는 우리 막내 영주, 함께 실험과 스터디를 하고 나면 늘 맛있는 과자로 우리 동기들의 에너지를 충전해주는, PS 고수이면서 손이 빠른 란희, 1학기 때 저의 소중한 샘플링 파트너였던, LC, comet, PBMC를 같이 배우는 동안 시험을 함께 겪고, 실험에 있어서는 저를 많이 도와준 착하고 배려심 많은 천사 형윤이. 2년 동안 힘이 들 때에는 잘 버틸 수 있게 해주고, 기분이 좋지 않을 때에는 금방 잊게 해주었던, 모든 희로애락을 함께 해준 우리 동기들! 2년은 정말 짧은 시간이었지만, 이제는 우리가 같이 만든 수많은 소중한 추억과 기쁨을 영원이라는 긴 시간으로 기억하겠습니다. 감사합니다.

이미 졸업을 했음에도 불구하고 저를 많이 격려하고 도와줬던 미향 누나, 샘

누나, 정현 누나, 화진 누나, 윤주에게도 고마운 마음을 전해주고 싶습니다. 함께 실험과 스터디를 하며 즐거운 시간을 보내던 위 학기 선배들에게 또한 감사드립니다. 연구실의 모든 선후배를 위해 늘 기도하며 축복해드릴 것입니다.

외아들임에도 불구하고 고향을 떠나서 몇 년간 외국에서 공부를 했기에 아빠, 엄마에게 정말 죄송스러운 마음이 듭니다. 집에 자주 가지 못하고 걱정을 늘 끼쳐드리는 것 같아서 송구스러운 마음을 항상 가지고 있었습니다. 유학이라는 큰 결정을 허락해주시고 언제나 제 의견을 들어주시며 아낌없는 사랑과 지지를 해주시는 친구 같은 아빠, 엄마에게 고맙다고 말하고 싶습니다. 우리가 함께 겪었던 어려움, 만났을 때의 행복한 웃음 그리고 이별할 때의 서운한 눈물…이 모든 것은 제 구학의 길에 큰 힘이 될 것입니다. 저도 아빠, 엄마의 자랑스러운 아들이 되기 위해 끝없이 노력하겠습니다.

8년간의 한국 생활 동안 저를 위해 기도해주시고 생활과 연구실 임상시험 대상자 모집에 많은 도움을 주신 서대문교회 형제, 자매님들께 고마운 마음을 전해드리고 싶습니다. 그리고 외로운 타국 생활을 하는 저에게 가족 같은 존재인, 저를 도와주고 또한 신앙생활을 올바르게 할 수 있도록 해준, 교회의 훌륭한 청년들에게도 고맙습니다.

이제 연세대학교에서의 6년 동안의 학교생활이 끝나가고 있습니다. 한국에 입국하면서부터 어학연수, 학부 그리고 대학원을 무사히 졸업하기까지, 이 모든 것을 이끌어주신 하나님께 제일 깊은 고마운 마음이 있습니다. 제 연약함을 잘 아시는 하나님께서, 사랑으로 구원과 지혜, 그리고 모든 어려움을 이겨내는 용기와 능력을 주셨기에 진심으로 감사드립니다. 앞으로도 하나님의 사람으로서 청결한

마음을 가진 예배자로서 하나님께서 이끌어주신 길을 따라 살아가겠습니다. 하나님, 감사합니다, 사랑합니다.

고맙고 또 고마운 마음으로 이 논문을 바칩니다.

2017년 12월

손 요

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ABBREVIATION

ADA	American Diabetes Association
AGE	Advanced glycation end product
ALE	Advanced lipoxidation end products
bp	Base pair
BMI	Body mass index
BP	Blood pressure
gDNA	Genomic DNA
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HOMA	Homeostasis-model assessment
hs-CRP	High-sensitivity C-reactive protein
HWE	Hardy-Weinberg equilibrium
IFG	Impaired fasting glucose
IR	Insulin resistance
K-CHIP	Korean Chip
KNHNES	Korean National Health and Nutrition Examination
LDL	Low density lipoprotein
M1dG	MDA-deoxyguanosine
MDA	Malondialdehyde

NFG	Normal fasting glucose
OGTT	Oral glucose tolerance test
PPAR	Peroxisome proliferator- activated receptor
PPARD	Peroxisome proliferator-activated receptor delta gene
ROS	Reactive oxygen species
RXR	Retinoic acid receptor
SNP	Single nucleotide polymorphism
T2D	Type 2 diabetes
WHO	World Health Organization

ABSTRACT

PPARD rs7770619 polymorphism in a Korean population: association with plasma malondialdehyde and impaired fasting glucose or newly diagnosed type 2 diabetes

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Aims: To determine whether peroxisome proliferator-activated receptor delta gene (*PPARD*) is a candidate gene for impaired fasting glucose (IFG) or type 2 diabetes (T2D) and whether it is associated with plasma malondialdehyde (MDA) concentrations.

Methods: A total of 1,798 study participants with normal fasting glucose (NFG), IFG, and newly diagnosed T2D were included. Among the ten single nucleotide polymorphisms (SNPs) that were most strongly associated with MDA, the rs7770619 polymorphism was identified in the *PPARD*.

Results: The CT genotype of the rs7770619 was associated with a lower risk of IFG + T2D after adjustments for age, body mass index (BMI), smoking, and alcohol use. A

significant association was observed between plasma MDA levels and the rs7770619 among the control (p<0.001) subjects and IFG + T2D (p=0.020) patients. Subjects with a CT genotype showed significantly lower MDA levels than the subjects with a CC genotype among both the control and IFG + T2D groups. Serum glucose levels and the rs7770619 were significantly associated in the controls (p<0.001), and a trend toward an association between serum glucose levels and rs7770619 was observed in IFG + T2D patients (p=0.088). Subjects with a CT genotype showed significantly lower serum glucose levels than subjects with a CC genotype in the control group.

Conclusions: The *PPARD* rs7770619 C>T SNP is a novel candidate variant for IFG and T2D based on the association between *PPARD* and MDA.

Keywords: *PPARD*; polymorphism; malondialdehyde; impaired fasting glucose; type 2 diabetes

1. Introduction

Hyperglycemia generates reactive oxygen species, which in turn damage cells in many ways [1]. Lipids are a primary target of reactive oxygen species. Peroxidation of lipids produces highly reactive aldehydes including malondialdehyde (MDA). MDA has been reported as a primary biomarker of free-radical-mediated lipid damage and oxidative stress [2]. Increased MDA levels in plasma, serum, and many other tissues have been reported in diabetic patients [3-5]. Increased lipid peroxidation presents a close relationship with the high glycemic levels and oxidative stress observed in patients with diabetes mellitus [4, 6].

The peroxisome proliferator-activated receptor delta gene *(PPARD*) might be an important candidate gene for type 2 diabetes (T2D) [7]. The association among *PPARD* variation, the risk of T2D, and related traits has been previously investigated. Although no association between the variants of *PPARD* and T2D was observed in a Korean population, several positive associations of polymorphisms with fasting plasma glucose and body mass index (BMI) were found in non-diabetic subjects [8]. Due to the close relationship observed between glucose in control subjects and MDA levels in hyperglycemic subjects [1, 5], a single nucleotide polymorphism (SNP) associated with plasma MDA that was identified using the Korean Chip (K-CHIP) could also be a novel SNP associated with impaired fasting glucose (IFG) or T2D risk. The K-CHIP was developed as a low-cost customized chip that is optimized for genetic studies on diseases and complex traits of the Korean population. Therefore, the objective of the present study

was to determine whether *PPARD* is a candidate gene for T2D by identifying an association between *PPARD* and the MDA level, which is considerably increased in hyperglycemic patients [5].

2. BACKGROUND

2.1. Prediabetes and type 2 Diabetes (T2D)

2.1.1. The prevalence of T2D

T2D, one of rapidly increased worldwide pandemic chronic diseases, became a global healthy issue in recent decades [9, 10]. The number of worldwide T2D patients is expected to increase up to 360 million by 2030 from 177 million in 2000 [9]. The similar trend is seen in Korea as well [9] According to the result of Korean National Health and Nutrition Examination (KNHANES) the prevalence of diabetes mellitus in adults aged 30 more increased from 8.6% in 2001 to 11.0% in 2013 [11]. Among the Korean population aged ≥20 the prevalence is expected to increase to approximately 5.5 million by 2030, which is almost 10.9% of the adult population of Korea (Fig. 1) [12].

Furthermore, complications of diabetes mellitus such as neuropathy, nephropathy, retinopathy, cardiovascular diseases, and cerebrovascular diseases, are increasing the morbidity, disability, and mortality [13]. Patients with diabetes are suffering severe health problems including physical, psychological and social disorder in their life [14]. In 2010, approximately 1.3 million of death related to diabetes occurred all over the world, which is as many as it occurred in 1990 [15]. The rate of death among patients with diabetes is about twice as high as that among persons without diabetes [16]. Diabetic complications cause some additional costs of healthcare, including emergency

or long-term medical expenses, aggravating both individual and national economic burden [13, 17].

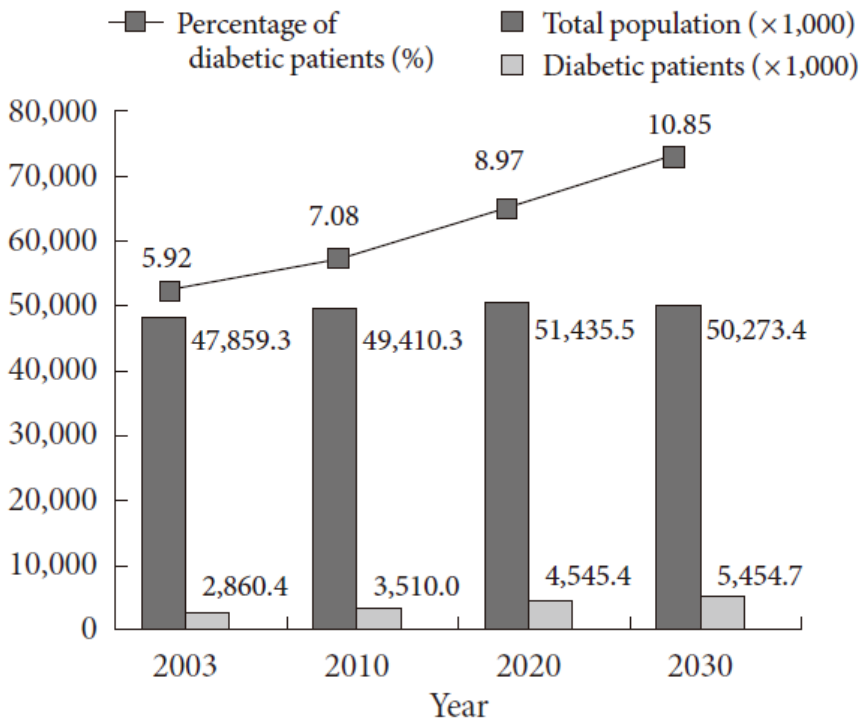

Figure. 1 Diabetic population estimates from 2003 to 2030 in Korea (Adapted from [12])

2.1.2. Diagnosis of diabetes

The diagnosis of diabetes mellitus is based on plasma glucose criteria, either the fasting plasma glucose or the 2-h value in the 75g oral glucose tolerance test (OGTT), and the hemoglobin A1c (HbA1c) test [18]. Based on the criteria of American Diabetes Association (ADA), individuals can be diagnosed with diabetes mellitus if:

1) They have diabetic symptoms, like polyuria, polydipsia, unexplained weight loss, and random plasma glucose level ≥200 mg/dL (11.1 mmol/L)

2) They have fasting glucose level ≥126 mg/dL (7 mmol/L)

3) Their Plasma glucose level after oral glucose tolerance test with a 2-hour post load (glucose 75g) ≥200 mg/dL (11.1 mmol/L)

4) Their HbA1c ≥6.5% [18, 19]

2.1.3. Impaired fasting glucose (IFG)

IFG, a component of metabolic syndrome, is not only an independent link with T2D [20]. IFG itself is an independent risk factor of cardiovascular disease like hypertension, dyslipidemia, coronary artery calcification, and subclinical atherosclerosis [20, 21]. According to the World Health Organization (WHO) criteria, individuals with IFG have a normal oral glucose tolerance test with a 2-hour post load (glucose 75g) level <140 mg/dL and fasting plasma glucose level ranging between ≥100 mg/dL (6.1 mmol/L) and <126 mg/dL (7.0 mmol/dL) [22]. ADA introduced HbA1c 5.7~6.4% as a new item for high diabetes risk [23].

2.2. Malondialdehyde (MDA)

MDA, a 3-carbon, low molecular weight active aldehyde, is one of the most frequently used markers of lipid peroxidation [24, 25]. MDA is produced when reactive oxygen species (ROS) degrade cell membrane polyunsaturated lipids (Fig. 2) [26, 27]. The maillard reactions and advanced lipid peroxidation reactions cause the biochemical modification of tissue proteins and lead to the formation of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs), which are associated with many age-related chronic disease, like atherosclerosis, uremia, diabetic complications, neurodegenerative disease, and normal physiological aging.

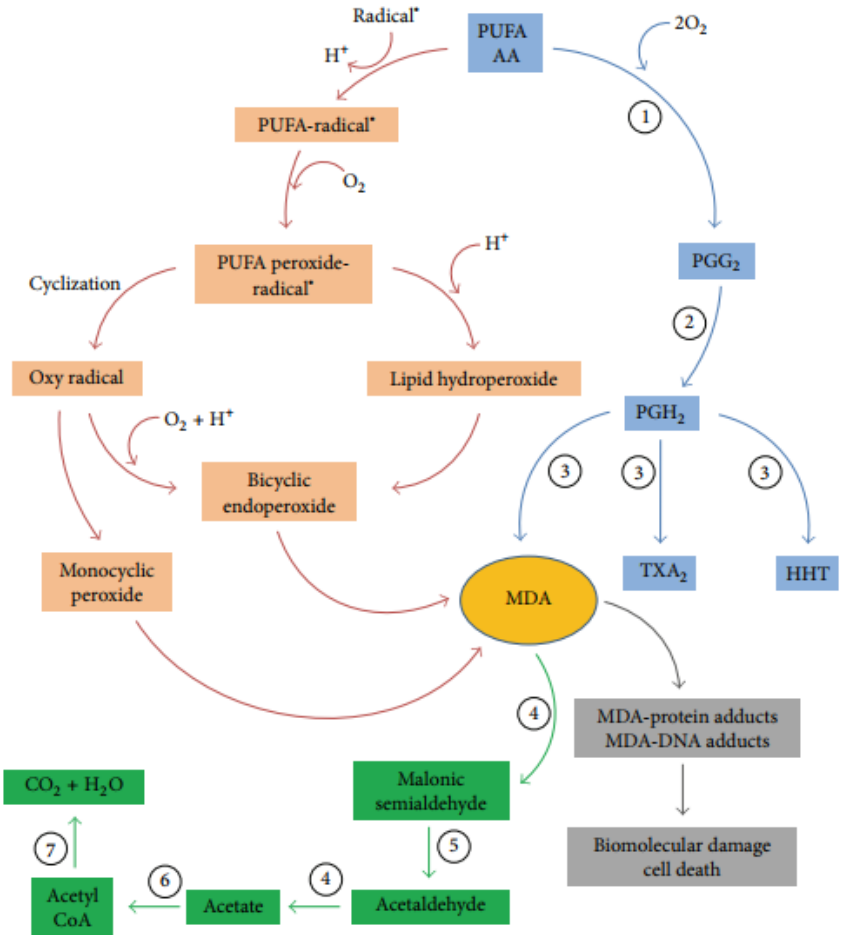

Figure. 2 MDA formation and metabolism (Adapted from [27])

MDA can also induce the formation of DNA adducts which leads to mutagenesis [28]. Since DNA is believed to be the target molecule for carcinogens, endogenous DNA adducts derived from oxidative stress, lipid peroxidation, and other sources have been proposed to contribute to the etiology of human cancers [29, 30]. DNA damage can arise due to the covalent binding of MDA to guanine and form MDA-DNA adduct (M1dG) (Fig. 3) [31-33]. The level of M1dG has been employed as an indicator of cancer-associated oxidative DNA damage [31] causing base pair substitutions and frameshift mutations, as well as arresting transcription [34]. Increased levels of MDA were detected in the urine of people with dysplasia and in the serum of cancer patients compared with noncancer controls in breast cancer studies [35, 36].

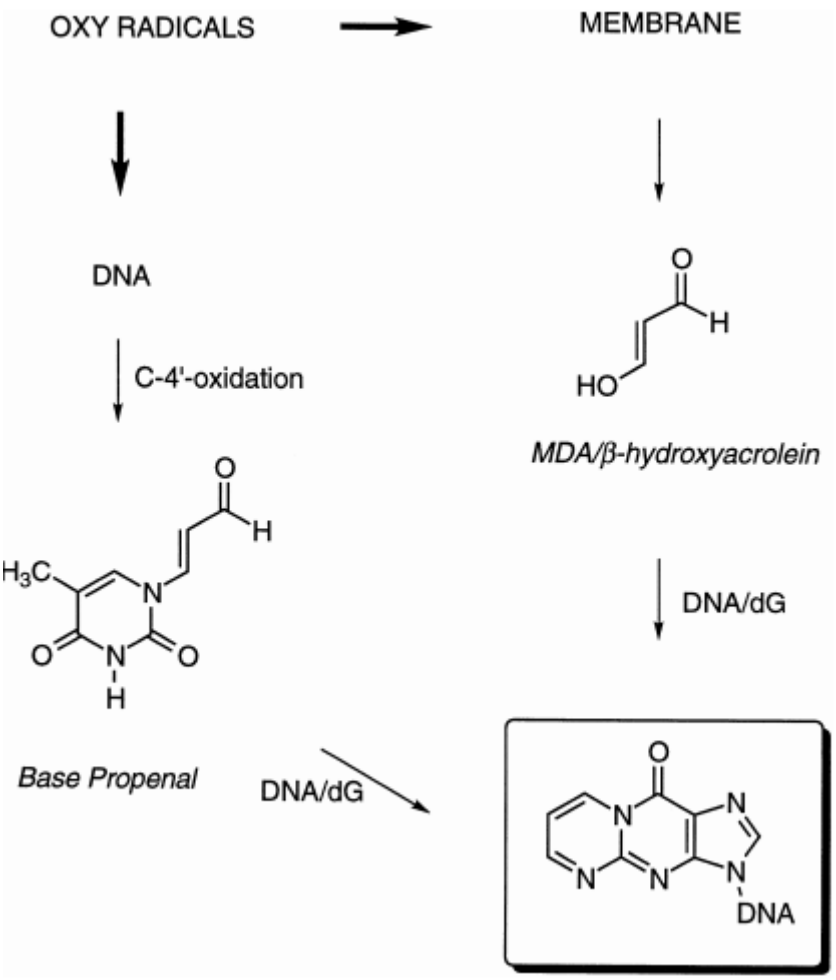

Figure. 3 Reaction of oxidizing agents with DNA to form M1dG (Adapted from [33])

2.3. Peroxisome proliferator-activated receptor delta gene (*PPARD*)

2.3.1. Prevue of PPARD

PPARD, a member of peroxisome proliferator- activated receptors (PPAR), which can be expressed in different tissues, including tissues relevant to metabolism, functioning as a transcription factor [37-39]. *PPARD* directly or indirectly activates the transcription of the genes associated with metabolism and it is highly likely that PPARδ directly or indirectly activates the transcriptional factors such as PPARγ, adiponectin, in cooperation with retinoic acid receptor (RXR). PPARδ/RXR heterodimers bind to the DR-1 type response elements with a core sequence AGGTCA on target gene promoters and turn on transcription upon ligand activation. *PPARD* controls many metabolic programs in glucose and fatty acid homeostasis through this direct transcriptional regulation (Fig. 4) [40].

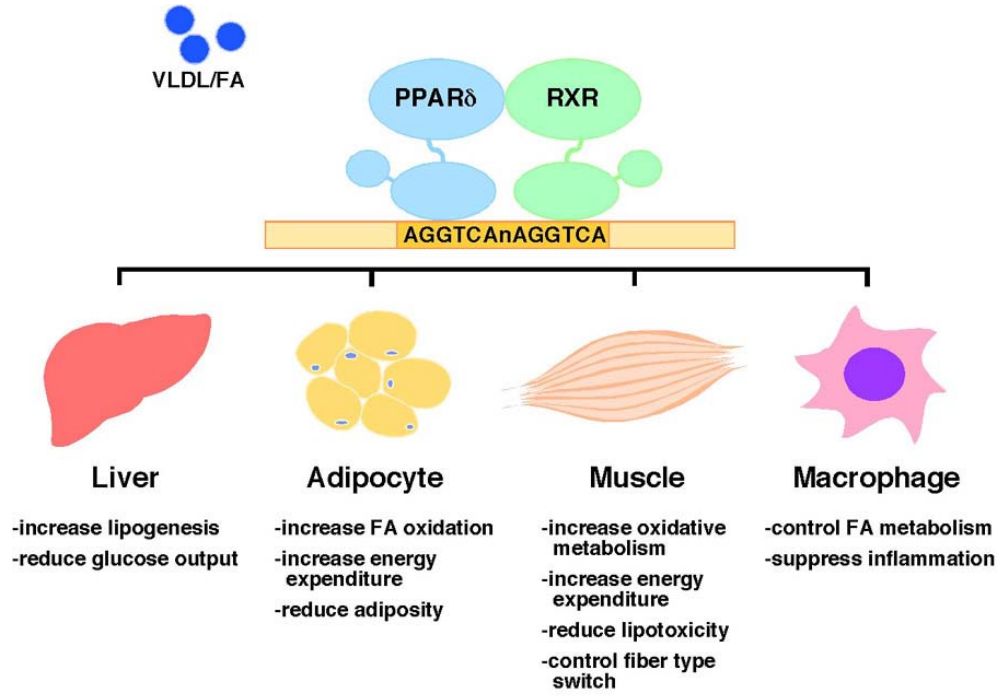

Figure. 4 Transcriptional regulation of metabolic homeostasis by *PPARD*

(Adapted from [40])

2.3.2. Functions of *PPARD*

The functions of *PPARD* and mechanism remain largely mysterious [37-39]. *PPARD* has been detected to play a crucial role in fatty acid β-oxidation in skeletal muscle and adipose tissue, and mostly expressed in skeletal muscle [41]. In obese animal models, synthetic *PPARD* was seen in promoting increase serum high density lipoprotein (HDL) while lowering triglyceride levels [42]. Transgenic mice with gain-of-function of expressing active form of *PPARD* in adipose tissue showed a decrease in lipid accumulation in both adipose tissue and serum [43]. In mice, *PPARD* is involved in pancreatic β-cell proliferation and insulin secretion [44]. Furthermore, ligands for *PPARD* have been proposed to be potential insulin sensitizers, based on improvements in standard glucose-tolerance tests [38]. *PPARD* knocked mice showed glucose intolerance and were prone to obesity [45].

In humans, genetic variants in *PPARD* in metabolism, obesity and diabetes have been found in innumerable studies in diverse population. Specific SNPs in *PPARD* show the association with effect of plasma triglyceride and HDL-cholesterol concentration, which are the risk factors of cardiovascular disease [46, 47].

As the functions of *PPARD* are still not known completely, there are no clear evidences that genetic variation in *PPARD* can affect the occurrence of T2D and metabolic syndromes. Both rodent and human data show that there is a likely mechanism for the effect that *PPARD* affects lipid and lipoprotein level due to the increase in skeletal

muscle fat oxidation [41, 42, 46, 47]. Coupling with the propose that the key mechanism of obesity and insulin resistance is due to an inability to oxidize fatty acid [48], *PPARD* might be a key target for the intervention and prevention of obesity and T2D.

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3. Materials and methods

3.1. Study population

A total of 2,167 study participants with normal fasting glucose (NFG), IFG, or newly diagnosed T2D were recruited from the Health Service Center during routine examinations at the National Health Insurance Corporation Ilsan Hospital in Goyang, Korea (January 2010-March 2015). The diagnosis of diabetes was based on the fasting plasma glucose level (≥126 mg/dL), and IFG was defined as a fasting plasma glucose level of 100-125 mg/dL. The exclusion criteria were a current diagnosis or history of cardiovascular disease, liver disease, renal disease, pancreatitis, or cancer as well as regular use of any medication. The aim of the study was carefully explained to all participants, who provided their written informed consent. The Institutional Review Board of Yonsei University and the National Health Insurance Corporation Ilsan Hospital approved the study protocol, which complied with the Declaration of Helsinki.

3.2. Laboratory experiments

Anthropometric measurements were performed on all participants; weights, heights, and BMIs were calculated in units of kilograms per square meter. Blood pressure (BP) was measured twice using an automatic BP monitor (FT-200S; Jawon Medical, Gyeongsan, Korea) after a resting period of at least 20 min, and the average value was used. For clinical chemistry assays, blood samples were obtained from each participant after a minimum fasting period of 12 h and were stored at –70°C until analysis was performed. The levels of fasting glucose, triglycerides, total-cholesterol, low density lipoprotein (LDL)-cholesterol, and HDL-cholesterol were measured using an automatic analyzer (Hitachi 7600 Autoanalyzer, Hitachi Ltd., Tokyo, Japan). The insulin levels were measured using an immunoradiometric assay kit from DIAsource ImmunoAssays S.A. (Louvain, Belgium). HbA1c was measured by immunoturbidimetric analysis. Insulin resistance (IR) was calculated by the homeostasis-model assessment (HOMA). Serum high-sensitivity C-reactive protein (hs-CRP) was measured using an ADVIA 2400 Clinical Chemistry System (Siemens Ltd., Tarrytown, NY, USA) and a commercially available, hs-CRP-Latex (II) X2 kit (Denka-Seiken Co., Ltd., Tokyo, Japan), and MDA was measured using an assay kit (TBARS Assay Kit; ZeptoMetrix Co., Buffalo, NY, USA) [49].

3.3. Affymetrix Axiom™ KORV1.0-96 array hybridization and SNP selection

A total of 2,167 samples were genotyped using the Axiom® 2.0 Reagent Kit (Affymetrix Axiom® 2.0 Assay User Guide; Affymetrix, Santa Clara, CA, USA) according to the manufacturer's protocol. Approximately 200 ng of genomic DNA (gDNA) was amplified and randomly fragmented into 25- to 125-base pair (bp) fragments. The gDNA was initially amplified in a 40-μL reaction containing 20 μL of a 10-ng/μL genomic DNA stock and 20 μL of a master mix. The initial amplification reaction conditions consisted of a 10-min initial amplification at room temperature, followed by amplification with 130 μL of Axiom 2.0 Neutral Solution, 225 μL of Axiom 2.0 Amp Solution and 5 μL of Axiom 2.0 Amp Enzyme. The amplification reactions were performed for 23±1 h at 37°C. The amplification products were analyzed in an optimized reaction to amplify fragments between 200 and 1100 bp in length. A fragmentation step reduced the amplified products into segments of approximately 25-50 bp in length, which were end-labeled using biotinylated nucleotides. After hybridization, the bound target was washed under stringent conditions to remove the non-specific background and to minimize the background noise caused by random ligation events. Each polymorphic nucleotide was queried in a multicolor ligation event conducted on the array surface. After ligation, the arrays were stained and imaged using a GeneTitan MC Instrument (Affymetrix, Santa Clara, CA, USA). The images were analyzed using the Genotyping Console™ Software (Affymetrix, Santa Clara, CA, USA). The genotype data were produced using the K-CHIP available through the K-

CHIP consortium. The K-CHIP was designed by the Center for Genome Science at the Korea National Institute of Health (4845-301, 3000-3031). Samples with the following inclusion thresholds were excluded: sex inconsistency, markers with a high missing rate (>5%), individuals with a high missing rate (>10%), minor allele frequency <0.01, and a significant deviation from the Hardy-Weinberg equilibrium (HWE) (p<0.001). SNPs in linkage disequilibrium with each other were excluded.

3.4. Statistical analysis

Descriptive statistical analyses were performed using SPSS version 23.0 (IBM, Chicago, IL, USA). The mean values are expressed as the mean ± standard error (SE), and a two-tailed value of $p<0.05$ was considered statistically significant. An independent *t*-test and Mann-Whitney *U*-test were performed for continuous variables to compare the parameters between the NFG controls and IFG or T2D patients. The HWE was assessed using PLINK version 1.07. The association between genotypes and MDA levels was evaluated using a linear regression analysis. The frequency was analyzed by a chi-squared test. The association of IFG or T2D with a genotype was calculated using the odds ratio (OR) [95% confidence intervals (CIs)] of a logistic regression model with an adjustment for confounding factors.

4. RESULTS

The clinical and biochemical characteristics of the NFG controls (*n*=1,210) and IFG or newly diagnosed T2D patients (*n*=588) are shown in Table 1. The case subjects were significantly older and heavier than the control subjects. After adjusting for age, sex, BMI, smoking, and drinking status, the case subjects showed higher systolic BP, triglyceride, glucose, HbA1c, and MDA values.

A total of 395,787 SNPs and 1,845 samples were used in subsequent analyses. The SNPs with the strongest associations with MDA were determined, and one SNP was identified in the *PPARD* (*p*=1.43E-07); therefore, we conducted an association analysis of rs7770619 in the *PPARD*.

Table 1. Clinical characteristics and frequencies of *PPARD* rs7770619 in NFG controls and patients with IFG or newly diagnosed T2D

	NFG control (*n*=1210)	IFG + T2D (*n*=588)	p^a	p^b
Age (year)	47.9±0.30	53.6±0.41	<0.001	-
BMI (kg/m^2)	23.8±0.08	24.9±0.12	<0.001	-
Systolic BP (mmHg)	119.6±0.44	127.0±0.67	<0.001	<0.001
Diastolic BP (mmHg)	75.5±0.33	79.0±0.43	<0.001	0.094
Triglyceride (mg/dL)†	118.1±2.02	143.3±3.39	<0.001	<0.001
Total-cholesterol (mg/dL)†	198.9±1.02	200.5±1.53	0.445	0.315
HDL-cholesterol (mg/dL)†	54.6±0.39	51.6±0.53	<0.001	0.526
LDL-cholesterol (mg/dL)†	121.2±0.93	122.0±1.42	0.854	0.075
Glucose (mg/dL)†	86.9±0.21	118.2±1.01	<0.001	<0.001
Insulin (μIU/dL)†	9.01±0.12	9.25±0.25	0.603	0.282
HOMA-IR†	1.94±0.03	2.71±0.09	<0.001	<0.001
HbA_{1c} (%)†	5.69±0.02	6.42±0.05	<0.001	<0.001
hs-CRP (mg/dL)†	1.25±0.09	1.55±0.12	0.081	0.082
Malondialdehyde (nmol/mL)†	8.23±0.07	10.9±0.23	<0.001	<0.001
***PPARD* rs7770619, *n* (%)**				
CC	1,127 (93.1)	581 (98.8)		
CT	83 (6.9)	7 (1.2)	<0.001	
TT	0 (0)	0 (0)		
T allele frequency	83 (3.4)	7 (0.6)	<0.001	

Mean ± SE. †tested by logarithmic transformation. *p*-values derived from an independent *t*-test. p^a; Unadjusted. p^b; Adjusted for age, sex, BMI, smoking, and drinking.

4.1. Distribution of the *PPARD* rs7770619 C>T polymorphism

The observed and expected frequencies of the *PPARD* rs7770619 C>T polymorphism were in HWE among the entire population. The relative frequencies of *PPARD* rs7770619 C>T genotypes in IFG + T2D patients significantly differed from those of the controls (Table 1). No homozygous mutation TT genotype was found in either the control or case groups. The frequency of the T allele of the *PPARD* rs7770619 C>T polymorphism in the case patients (0.006) was significantly lower than that in the control subjects (0.034) (p<0.001) (Table 1). The presence of the CT genotype was associated with a decreased risk of IFG + T2D [OR 0.164 (95% CI 0.075-0.356), p<0.001] (Fig. 5). The significance of the association remained after adjusting for age, sex, BMI, smoking, and drinking status [OR 0.168 (95% CI 0.095-0.296), p<0.001].

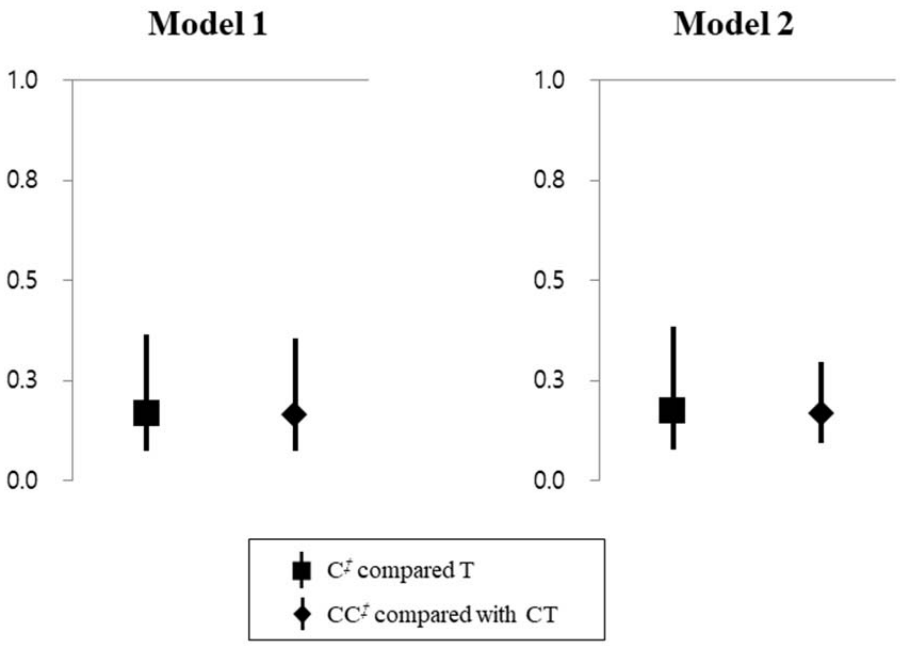

Figure 5. Unadjusted and adjusted odds ratios for all patients with IFG and T2D according to the *PPARD* rs7770619 genotypes.

‡Reference. CI, confidence interval. Model 1: unadjusted; Model 2: adjusted for age, sex, BMI, smoking status, and drinking status.

4.2. Association of plasma MDA and serum glucose with the *PPARD* rs7770619 C>T polymorphism

A significant association was observed between plasma MDA levels and *PPARD* rs7770619 C>T polymorphism in the controls (CC: 8.30±0.07 nmol/mL; CT: 7.23±0.20 nmol/mL; $p<0.001$) and IFG + T2D patients (CC: 10.9±0.24 nmol/mL; CT: 7.14±1.26 nmol/mL; $p=0.020$) (Fig. 6). Subjects with the CT genotype had significantly lower MDA levels than subjects with the CC genotype among both the control subjects and IFG + T2D patients. The serum glucose level and the *PPARD* rs7770619 C>T polymorphism were significantly associated in the controls (CC: 87.1±0.22 mg/dL; CT: 83.9±0.75 mg/dL; $p<0.001$), and a trend toward an association between serum glucose and the *PPARD* rs7770619 C>T polymorphism was observed in IFG + T2D cases (CC: 118.3±1.02 mg/dL; CT: 106.3±2.03 mg/dL; $p=0.088$). Subjects with a CT genotype showed significantly lower serum glucose levels than subjects with a CC genotype in the control group (Fig. 6).

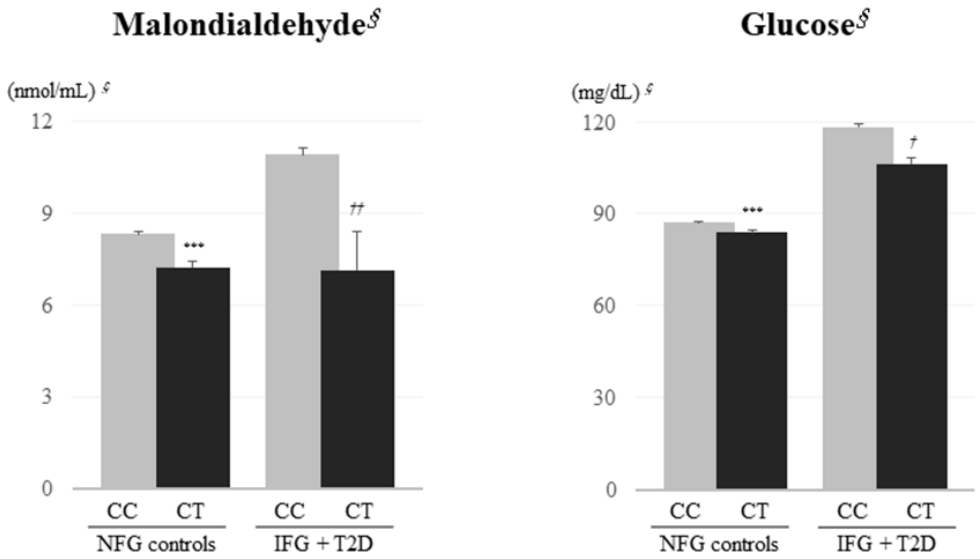

Figure 6. Relationship between *PPARD* rs7770619 and plasma MDA and between *PPARD* rs7770619 and serum glucose in NFG controls and IFG + T2D patients.

Mean ± SE. §Tested using logarithmic transformation. $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$ derived from an independent *t*-test of the NFG controls. $^{\dagger}p<0.1$ and $^{\dagger\dagger}p<0.05$ derived from a Mann-Whitney *U*-test of the IFG + T2D group.

5. DISCUSSION

The polymorphism of genes related to plasma MDA might influence the susceptibility to T2D due to the relationship between glucose and MDA levels [1, 5]. In the current study, we discussed the potential relationship between the *PPARD* rs7770619 polymorphism and T2D susceptibility in Korean populations. The major finding is that the frequency of the *PPARD* rs7770619 CT genotype was significantly lower in IFG + T2D patients than in the controls, suggesting an association between the *PPARD* rs7770619 C>T SNP and IFG or T2D. This observation is consistent with the recent finding that the *PPARD* polymorphism has emerged as a key player the development of T2D [50]. The *PPARD* rs7770619 C>T SNP is considered to be functional because serum glucose levels and the *PPARD* rs7770619 C>T polymorphism were significantly associated in the control group in this study. The significance of the present observations is underscored by the association of *PPARD* locus polymorphism with altered glucose and plasma MDA, which is a reliable oxidative stress marker during hyperglycemia [1].

PPARs are transcription factors that belongs to the ligand-activated nuclear receptor superfamily [51]. The PPAR family is consisted of three subtypes: *PPARα, PPARδ (*or *PPARβ*), and *PPARγ*. It has been summarized that *PPARα* mainly involved in lipid metabolism with oxidation process of liver cells. *PPARγ* plays a major role in fatty acid storage and glucose metabolism [37, 52, 53] and the genes activated by *PPARγ* stimulate lipid uptake and adipogenesis. Among the three subtypes, *PPARδ* is the least explored and its functions are still debatable. The activation of *PPARδ* relieves dyslipidemia,

hyperglycemia, and IR in diabetes and obesity [54]. Distinct from *PPARα* and *PPARγ, PPARδ* extensively expressed in organs and tissues, particularly within the pancreatic islets [37]. *PPARδ* also stimulates the proliferation of pancreatic β-cells and insulin secretion in mice, thereby, pancreatic β-cells can be protected from damage of free fatty acids [52, 55, 56]. However, the underlying mechanisms for the association between *PPARD* rs7770619 and T2D still remain to be elucidated. *PPARδ* regulates glucose homeostasis and insulin signaling in various tissues [57, 58, 59]. Previous studies shown that *PPARδ* activation in db/db mice improves hepatic and peripheral glucose metabolism and insulin sensitivity [60], in addition, *PPARδ* agonists exert beneficial effects on improving IR in both genetic and diet induced mice [38]. Nevertheless, we failed to provide evidence for the association between *PPARD* rs7770619 and the HOMA-IR; only the serum glucose level was demonstrated to be significantly different between genotypes. Moreover, the evidence from an in vitro study indicated that the *PPARδ* agonist directly improves glucose metabolism via an insulin-independent mechanism with phosphorylation of AMPK and p38 MAPK [61].

Hyperglycemia generates reactive oxygen species [1, 5]. The increase in plasma MDA levels indicated that any sufficiently incurred oxidative stress could cause free-radical-mediated peroxidation of lipid components in the cell membrane; thus, MDA is a good indicator for evaluating oxidative stress in degenerative diseases such as T2D [62]. In this study, the patients with IFG or newly diagnosed T2D exhibited a higher concentration of plasma MDA than the control subjects. Subjects with the *PPARD* rs7770619 CT genotype showed significantly lower fasting glucose levels than those

with the CC genotype in the control group. Additionally, the IFG + T2D patients with the CT genotype showed a decreased tendency in serum glucose levels compared with those with the CC genotype. Furthermore, the significantly lower concentration of plasma MDA in subjects carrying the CT genotype compared to those with the CC genotype in both groups could potentially explain the apparently lower risk of IFG or T2D associated with the *PPARD* rs7770619 CT genotype. Therefore, this study suggests that the *PPARD* rs7770619 C>T SNP is a candidate gene for IFG or T2D because of the association between *PPARD* and MDA, which is the primary biomarker of free-radical-mediated lipid damage and oxidative stress [2].

The strengths of the current study include an association between the *PPARD* rs7770619 polymorphism and T2D, which is combined with oxidative stress. Moreover, this study is the first to report the association between *PPARD* SNPs and oxidative stress markers. The present results share the limitations of cross-sectional observational studies because we only evaluated an association rather than making a prospective prediction. Additionally, the study specifically focused on a representative group of Koreans; therefore, the results cannot be generalized to other ethnic or geographical groups, and no replication was performed. In summary, our results show an intriguing association between the *PPARD* rs7770619 CT genotype and a decreased risk of IFG or T2D as well as reduced levels of oxidative stress. This result could suggest that the *PPARD* rs7770619 C>T SNP is a novel candidate gene for IFG or T2D through the association of *PPARD* and MDA, which is a reliable biomarker of oxidative stress and hyperglycemia.

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국문요약

한국인 인구집단에서의 *PPARD* rs7770619 다형성과 혈장 내 말론디알데하이드 농도, 공복혈당장애 혹은 새롭게 진단받은 당뇨병과의 관련성

연구목적 : 본 연구는 한국인 인구집단 대상으로 peroxisome proliferator-activated receptor delta 유전자 (*PPARD*)와 혈장 내 말론디알데하이드 농도 간의 관련성 분석하고 *PPARD* 유전자가 공복혈당장애 혹은 제 2형 당뇨병 위험 예측의 새로운 후보지표가 될 수 있는지 살펴보고자 한다.

연구방법 : 경기도 일산병원 건강검진센터에서 정상 공복혈당 대상자, 공복혈당장애가 있는 대상자, 새롭게 진단 받은 제 2형 당뇨병 환자를 포함한 1,798명의 피험자를 대상으로 진행하였다. 당뇨병 진단 기준은 공복혈당이 126 mg/dL이상 혹은 당화혈색소 6.5% 이상으로 하였고, 공복혈당장애는 공복혈당이 100 mg/dL에서 125 mg/dL 사이 혹은 당화혈색소가 5.7%에서 6.4% 사이의 범위로 하였다. 유전자형 자료는 Korean Chip을 통해 알 수 있었다. 산화적 스트레스 지표이며 공복혈당장애와 제2형 당뇨병의 생체지

표인 혈장 내의 말론디알데하이드 농도와 가장 관련성이 높은 10개의 단일염기 다형성 중에 rs7770619 다형성이 발견되었다.

연구결과 : 모두 대조군, 공복혈당장애과 제 2형 당뇨병 그룹에서 *PPARD* rs7770619 CT 유전자형을 가지고 있는 개체는 CC 유전자형보다 유의적으로 낮은 혈장 MDA 수준이 보였다. 대조군에서 CC 유전자형보다 CT유전자형 개체는 유의적으로 더 낮은 혈청 내 포도당 수준을 갖고 있고 *PPARD* rs7770619 C>T 다형성은 혈청 내 포도당 농도 사이에 유의적인 상관성을 보였다. *PPARD* rs7770619와 혈청 내 포도당 농도 사이의 상관성은 공복혈당장애와 제 2형 당뇨병 그룹에서도 비슷한 추세를 보였다.

연구결론 : 혈장 내 말론디알데하이드 농도와 *PPARD* 사이의 연관성을 통해 *PPARD* rs7770619 C>T SNP는 공복혈당장애와 제 2형 당뇨병 사이에 관련성이 있는 것으로 결론을 맺었다.

핵심되는 말 : *PPARD* 유전자; 단일염기다형성; 말론디알데하이드; 공복혈당장애; 제 2형 당뇨병