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Influence of cigarette smoking and inflammatory gene polymorphisms on glycated hemoglobin in the Japanese general population

Yuichiro Nishida [a,*], Megumi Hara [a], Tatsuhiko Sakamoto [b], Koichi Shinchi [c], Sayo Kawai [d], Mariko Naito [d], Nobuyuki Hamajima [e], Aya Kadota [f], Sadao Suzuki [g], Rie Ibusuki [h], Akie Hirata [i], Miwa Yamaguchi [j], Nagato Kuriyama [k], Isao Oze [l], Haruo Mikami [m], Michiaki Kubo [n], Hideo Tanaka [l]
for the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study Group

[a] Department of Preventive Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan
[b] Tosu Public Health and Welfare Office, Saga Prefectural Government, 1234-1 Moto-machi, Tosu 841-0051, Japan
[c] Division of International Health and Nursing, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan
[d] Department of Preventive Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
[e] Department of Healthcare Administration, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
[f] Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Setatsukinowa-cho, Otsu 520-2192, Japan
[g] Department of Public Health, Nagoya City University Graduate School of Medical Science, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
[h] Department of International Island and Community Medicine, Kagoshima University Graduate School of Medical and Dental Science, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan
[i] Department of Geriatric Medicine, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maedashi, Higashi-ku, Fukuoka 812-8582, Japan
[j] Department of Preventive Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
[k] Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachidori Hirokojiagaru, Kamigyo-ku, Kyoto 602-8566, Japan
[l] Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
[m] Division of Cancer Registry, Prevention and Epidemiology, Chiba Cancer Center, 666-2 Nitona-cho, Chuo-ku, Chiba 260-8717, Japan
[n] Laboratory for Genotyping Development, Center for Genomic Medicine, RIKEN, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama 230-0045, Japan

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ABSTRACT

Objective. Inflammation is closely involved in the development of type 2 diabetes, and cigarette smoking acts as potent inducer of inflammation. We therefore investigated interactions between inflammation-related gene polymorphisms and cigarette smoking on glycated hemoglobin (HbA_{1c}) in the Japanese general population.

Method. We conducted a cross-sectional study using data collected from 2619 Japanese (1274 males and 1345 females) 40–69 years of age who participated in baseline survey of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study (2005–2008). Eight polymorphisms in seven genes (interleukin [*IL*]-*1β*, *IL-2*, *IL-4*, *IL-8*, *IL-10*, *IL-13* and tumor necrosis factor-α) were determined using the Invader assay. The interactions of smoking and gene polymorphisms on HbA_{1c} levels were analyzed using multiple linear and logistic regression models and analysis of covariance with adjustment for potential confounders.

Results. Among the eight polymorphisms, only one significant interaction was detected for *IL-1β* T-31C ($P < 0.0001$). Among the subjects carrying TT genotype, current heavy smokers (≥20 cigarettes/day) had higher HbA_{1c} (5.83 [95% confidence interval 5.67–5.99] %) versus all other smoking status groups (never 5.49 [5.41–5.56] %, former 5.54 [5.43–5.65] %, current moderate [<20 cigarettes/day] 5.50 [5.30–5.69] %), whereas such differences were not observed in the subjects with C allele. The logistic regression analyses regarding high-normal HbA_{1c} levels showed a similar pattern of results.

Conclusion. Smoking status did not interact with any other inflammation-related polymorphisms except for *IL-1β* T-31C. Heavy smokers harboring the TT genotype of *IL-1β* T-31C polymorphism show a greater adverse effect of smoking on HbA_{1c} levels among Japanese middle-aged subjects.

1. Introduction

Inflammation plays a critical role in the pathogenesis of type 2 diabetes (Shoelson et al., 2006). The elevation of plasma inflammatory cytokines (IL-1β and IL-6) precedes the development of type 2

* Corresponding author.
E-mail address: ynishida@cc.saga-u.ac.jp (Y. Nishida).

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diabetes (Spranger et al., 2003). Inflammation occurs not only systemically, but also locally within insulin-sensitive tissues (e.g., liver and skeletal muscle) and the pancreas. Inflammatory cytokines act locally to interfere with insulin signaling at sites where they are produced, and local inflammation can induce β cell dysfunction and subsequent insulin deficiency in the pancreatic islets of subjects with type 2 diabetes mellitus (Shoelson et al., 2006; Esser et al., 2014).

Cigarette smoking is an environmental factor that potently induces an inflammatory response. It is known that smokers have higher levels of circulating inflammatory cytokines, such as IL-6, IL-8 and TNF-α, than nonsmokers (Iho et al., 2003; Bermudez et al., 2002; Petrescu et al., 2010). In an in vitro study, cigarette smoke condensate treatment increased the expression levels of the *IL-1β* and *IL-8* genes in normal human bronchial epithelial cells, in which the degree of *IL-1β* gene induction was greatest among the six cytokines examined (Hellermann et al., 2002). The chemical species derived from smoking, such as nicotine and cotinine, are detected in various biological samples including saliva, hair, blood and urine (Matsumoto et al., 2013), thus indicating that the toxic chemical species derived from cigarette smoke are absorbed from the lung capillaries and spread throughout the whole body to all organs, including insulin-sensitive tissues and the pancreas.

Polymorphisms in inflammatory genes have been shown to be involved in the modulation of the circulating inflammatory protein levels, such as C-reactive protein and IL-6 (Pankow et al., 2001; Jerrard-Dunne et al., 2004; Oberbach et al., 2008). Furthermore, it has been suggested that the degree of inflammatory response to cigarette smoking may differ according to individual's genotype for inflammatory genes (Jerrard-Dunne et al., 2004). Although both external (i.e., cigarette smoking) and internal (i.e., inflammatory-related gene polymorphisms) factors regulating inflammation have been shown to be associated with the development of type 2 diabetes and/or insulin resistance, respectively (Kawakami et al., 1997; Nakanishi et al., 2000; Wannamethee et al., 2001; Sairenchi et al., 2004; Willi et al., 2007; Fernandez-Real et al., 2000; Kubaszek et al., 2003; Achyut et al., 2007; Banerjee and Saxena, 2012), the interactions between inflammatory polymorphisms and smoking on the glycemic control remain to be elucidated. The glycated hemoglobin (HbA_{1c}) level reflects the mean plasma glucose level over the preceding 2–3 months (Rohlfing et al., 2002), and this clinical index is commonly used to obtain a diagnosis of diabetes.

The purpose of the current study was to investigate possible gene–environment interactions between several inflammation-related gene polymorphisms and cigarette smoking on the HbA_{1c} levels in the Japanese general population. We therefore conducted the current cross-sectional study to test the hypothesis that the association of cigarette smoking on the HbA_{1c} levels would be modified by polymorphisms of genes that encode inflammatory cytokine proteins.

2. Materials and methods

2.1. Subjects

In the current cross-sectional study, we analyzed data for 4512 Japanese subjects 40–69 years of age who voluntary participated in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study during the period of 2005–2008. The study subjects were recruited from 10 different areas throughout Japan. The J-MICC study was launched in 2005 to confirm and detect gene–environment interactions involved in the development of lifestyle-related diseases in the Japanese general population, and the details of this cohort are described in detail elsewhere (Hamajima and J-MICC Study Group, 2007; Wakai et al., 2011). The J-MICC study was conducted in accordance with the ethical guidelines for epidemiological research of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan. Written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committees at the Nagoya University Graduate School of Medicine and other institutions participating in the J-MICC study.

2.2. Questionnaire and measurements

Data on cigarette smoking, alcohol consumption, dietary habits, physical activity, as well as current medications and past disease history, were collected using a self-administered questionnaire. As for the smoking status, the subjects were first asked about their smoking status from the past to the present. Then, the current smokers were requested to report their usual cigarette consumption (cigarettes/day). The smoking status was categorized as never, former, current 1–19, or ≥20 cigarettes/day. In the present study, current smokers who smoked <20 cigarettes/day were described as moderate smokers, while current smokers who smoked ≥20 cigarettes/day were described as heavy smokers. The total energy intake and ethanol consumption were calculated using data obtained via a validated short food frequency questionnaire (FFQ) (Tokudome et al., 2004; Tokudome et al., 2005; Imaeda et al., 2007). Ethanol consumption was categorized as never, former, current 0.1–22.9, 23.0–45.9 or ≥46 g/day. The amount of habitual physical activity more than an intensity corresponding to 3 metabolic equivalents (METs) was assessed as previously described (Hara et al., 2012). A first-degree family history of diabetes was categorized as positive, negative or unknown. Anthropometric measurements and blood sampling were conducted as part of the health checkup or for research purposes at the institutions participating in the J-MICC study (Hamajima and J-MICC Study Group, 2007). Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was determined by dividing body weight in kilograms by the square of height in meters. The HbA_{1c} level was measured using a latex aggregation immunoassay (Japan Diabetes Society [JDS] value). The HbA_{1c} value was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated according to the following formula: HbA_{1c} (NGSP [%]) = 1.02 × HbA_{1c} (JDS [%]) + 0.25% (Kashiwagi et al., 2012). A significantly elevated HbA_{1c} (high-normal HbA_{1c}) level may be a superior clinical index for predicting the development of type 2 diabetes (American Diabetes Association, 2010). An HbA_{1c} level of 5.7% was used as a cut-off value to define a high-normal 5.7% (Heianza et al., 2011).

2.3. Genotyping

One hundred and seven single-nucleotide polymorphisms were genotyped using an Invader assay (Third Wave Technologies, Madison, WI, USA) (Ohnishi et al., 2001) at the Laboratory for Genotyping Development, Center for Genomic Medicine, RIKEN, as previously described (Wakai et al., 2011). Among 107 single-nucleotide polymorphisms, we selected eight polymorphisms in seven inflammatory genes for the current analyses (*IL-1β*: T-31C [rs1143627], *IL-2*: T-330G [rs2069762], *IL-4*: T-33C [rs2070874], *IL-8*: T-251A [rs4073], *IL-10*: T-819C [rs1800871], *IL-13*: C-1111T [rs1800925], *TNF-α*: T-1031C [rs1799964] and *TNF-α*: C-857T [rs1799724]). The genotype distributions of these eight polymorphisms did not deviate from Hardy–Weinberg equilibrium ($P > 0.05$) (Wakai et al., 2011). The *IL-6* C-634G polymorphism (rs1800796) was not selected because its genotype distribution deviated from Hardy–Weinberg equilibrium ($P < 0.05$) (Wakai et al., 2011).

2.4. Statistical analysis

In the current analysis, 1893 subjects were excluded due to following reasons: missing data on gene polymorphisms (*IL-1β*: n = 2, *IL-2*: n = 6, *IL-4*: n = 2, *IL-8*: n = 27, *IL-10*: n = 11, *IL-13*: n = 4, *TNF-α* T-1031C: n = 1, and *TNF-α* C-857T: n = 2), cigarette smoking status

(n = 5), HbA_{1c} (n = 1763), taking type 2 diabetes medications (n = 193) or having a dietary energy intake extraordinarily greater than 4000 kcal/day (n = 2). Consequently, 2619 subjects in seven investigation areas remained for the current analysis. Among these 2619 participants, there were subjects with missing data regarding alcohol consumption (20 males and 22 females), physical activity (9 males and 14 females), height (1 male), weight (1 male) and BMI (1 male).

The statistical analyses were performed using the SAS software program (version 9.3 for Windows, SAS Institute, Cary, NC, USA). A *P* value of <0.05 was considered to be statistically significant. Sex differences in baseline characteristics were examined using the *t* test for continuous variables or chi-square test for categorical variables. Because of the low frequency of current smokers among females, males and females were analyzed together and sex was included as an adjusted factor in the following multivariate analyses. Multiple linear and logistic regression analyses were performed to calculate the regression coefficients (β) and evaluate the associations (*P* trend) between the cigarette smoking status (as an independent variable) and either the HbA_{1c} level or a high-normal HbA_{1c} value (≥5.7%) (as dependent variables) according to each genotype of the eight polymorphisms. Adjustment was made for the following potential confounding factors: sex (categorical), age (continuous), BMI (continuous), energy intake (continuous), physical activity (continuous), alcohol drinking (categorical), first-degree family history of diabetes mellitus (categorical) and investigation site (categorical). The smoking status was coded as follows: never (0), former (1), current moderate (2) or current heavy (3), treated as a continuous variable. Then, to identify gene polymorphism(s) that can modify the associations between cigarette smoking and the HbA_{1c} level, interactions with gene polymorphisms were assessed by including an interaction term, indicated as "gene polymorphism (categorical)*smoking status (continuous)." The genotypes of the each polymorphism were coded as 0 for homozygous genotype, 1 for heterozygous genotype or 2 for the opposite homozygous genotype.

Given that our current purpose was to identify inflammatory polymorphisms that can modify the association of cigarette smoking with the HbA_{1c} level, and the interaction analysis was statistically significant only for the *IL-1β* T-31C polymorphism among the eight polymorphisms (Table 2), the subsequent analyses focused on the *IL-1β* T-31C polymorphism. The significance of univariate correlations between either the *IL-1β* T-31C polymorphism or smoking status and selected characteristics (e.g., age and BMI) was assessed according to Spearman's rank correlation coefficient. In the correlation analysis, a family history of diabetes was orderly coded as 0 (negative), 1 (unknown), or 2 (positive). To assess the associations of the *IL-1β* T-31C polymorphism and smoking status with the HbA_{1c} level, the adjusted mean value of HbA_{1c} and its 95% confidence interval (CI) according to the *IL-1β* T-31C genotype or smoking status group were computed as least square means using the general linear model procedure with the LSMEANS statement in SAS. In these analyses, adjustment was made for sex and age (model 1), with additional adjustment for BMI, energy intake, physical activity, alcohol drinking, first-degree family history of diabetes mellitus, investigation site, smoking status (for the evaluation of the influence of the *IL-1β* T-31C polymorphism on the HbA_{1c} level) or *IL-1β* T-31C polymorphism (for the evaluation of the influence of the smoking status on the HbA_{1c} level) (model 2). Similarly, the odds ratios (ORs) and 95% CIs of the *IL-1β* T-31C polymorphism and smoking status for a high-normal HbA_{1c} value (≥5.7%) were estimated using logistic regression models adjusted for confounding factors, as described above.

Furthermore, an analysis of covariance (ANCOVA) was used to calculate the adjusted mean HbA_{1c} value (and 95% CI) and compare the levels between the smoking status groups within each *IL-1β* T-31C genotype. In order to conduct a similar analysis on the risk of a high-normal HbA_{1c} level, the ORs for high-normal HbA_{1c} and their 95% CIs were also calculated using never smokers in each genotype as a reference group.

Table 1
Characteristics of study subjects by sex. The J-MICC Study 2005–2008.

(n = 2619)	Males (n = 1274)	Females (n = 1345)	P[a]
Age (years)	57.3 ± 8.6	56.9 ± 8.4	0.30
Height (cm)[b]	166.8 ± 6.1	154.0 ± 5.5	<0.01*
Weight (kg)[b]	66.1 ± 9.9	53.7 ± 7.6	<0.01*
BMI (kg/m^2)[b]	23.7 ± 3.0	22.6 ± 3.1	<0.01*
Energy intake (kcal/day)	1949 ± 355	1561 ± 259	<0.01*
Physical activity (MET h/day)[c]	13.4 ± 13.2	12.7 ± 11.5	0.17
Smoking, n (%)			
Never	348 (27.3)	1202 (89.4)	<0.01*
Former	563 (44.2)	57 (4.2)	
Current moderate 1–19 cigarettes/day	119 (9.3)	54 (4.0)	
Heavy ≥20 cigarettes/day	244 (19.2)	32 (2.4)	
Drinking, n (%)[d]			
Never	267 (21.3)	856 (64.7)	<0.01*
Former	28 (2.2)	23 (1.7)	
Current 0.1–22.9 g/day	450 (35.9)	389 (29.4)	
23.0–45.9 g/day	262 (20.9)	37 (2.8)	
46.0+ g/day	247 (19.7)	18 (1.4)	
Family history of diabetes, n (%)	189 (14.8)	215 (16.0)	0.36
HbA_{1c} (%)	5.54 ± 0.64	5.48 ± 0.49	<0.01*
TC (mg/dL)	205 ± 32	219 ± 35	<0.01*
HDL-C (mg/dL)	58 ± 16	68 ± 16	<0.01*

Values are expressed as the means ± standard deviation for continuous variables or number (percentage) for categorical variables. BMI, body mass index; MET, metabolic equivalent; HbA_{1c}, glycated hemoglobin; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol.

[a] *P* values for sex differences are based on *t* tests for continuous variables and chi-square tests for categorical variables.

[b] Based on 1273 males.

[c] Based on 1265 males and 1331 females.

[d] Based on 1254 males and 1323 females.

* $P < 0.05$.

3. Results

3.1. Characteristics of the study subjects

The characteristics of the study participants are shown in Table 1. Age was similar between males and females, while both BMI and energy intake were statistically significantly higher in males than females ($P < 0.01$). Cigarette smoking and alcohol drinking were more prevalent among males than females ($P < 0.01$). The percentages of participants who had a first-degree family history of diabetes were similar between the sex groups, while the HbA_{1c} levels were significantly higher in males than females ($P < 0.01$).

3.2. Interaction of inflammatory gene polymorphisms and cigarette smoking on the HbA_{1c} level and a high-normal HbA_{1c} value

Among the eight gene polymorphisms investigated, only one statistically significant interaction was found for the *IL-1β* T-31C polymorphism (*P* interaction < 0.0001), in which the *P* value was statistically significant even after using Bonferroni correction (Bonferroni-corrected $P < 0.0063$) (Table 2). None of the interactions between the other seven polymorphisms and cigarette smoking on the HbA_{1c} level were statistically significant (*IL-2*: $P = 0.66$, *IL-4*: $P = 0.78$, *IL-8*: $P = 0.08$, *IL-10*: $P = 0.09$, *IL-13*: $P = 0.50$, *TNF-α* T-1031C: $P = 0.74$, and *TNF-α* C-857T: $P = 0.74$). A similar pattern of results was obtained from the logistic regression analyses with respect to the risk of a high-normal HbA_{1c} value, although the *P* value was marginal for the interaction between the *IL-1β* T-31C

Table 2
Associations of smoking with HbA_{1c} or high-normal HbA_{1c} by each genotype of inflammatory polymorphisms, and interactions between smoking and gene polymorphism on the HbA_{1c} levels. The J-MICC Study 2005–2008.

Polymorphism	Genotype	HbA_{1c}				High-normal HbA_{1c}			
		β[a]	SE	*P* trend	*P* interaction[b]	β[a]	SE	*P* trend	*P* interaction[b]
IL-1β T-31C	CC (n = 584)	−0.0040	0.0254	0.88	<0.0001*	0.01	0.13	0.96	0.06
[rs1143627]	CT (n = 1274)	−0.0004	0.0166	0.98		−0.02	0.09	0.81	
	TT (n = 761)	0.0963	0.0292	0.001		0.24	0.10	0.02	
*IL-2*T-330G	TT (n = 1166)	0.0191	0.0214	0.37	0.66	0.10	0.09	0.28	0.54
[rs2069762]	TG (n = 1172)	0.0363	0.0189	0.05		0.12	0.09	0.18	
	GG (n = 281)	0.0533	0.0306	0.08		−0.21	0.20	0.29	
*IL-4*T-33C	TT (n = 1181)	0.0305	0.0197	0.12	0.78	0.02	0.09	0.84	0.96
[rs2070874]	TC (n = 1162)	0.0193	0.0206	0.35		0.11	0.09	0.24	
	CC (n = 276)	0.0450	0.0318	0.16		0.17	0.19	0.38	
*IL-8*T-251A	AA (n = 1205)	0.0456	0.0197	0.02	0.08	0.09	0.09	0.29	0.97
[rs4073]	AT (n = 1150)	0.0124	0.0186	0.51		0.07	0.09	0.42	
	TT (n = 264)	0.0768	0.0484	0.11		0.10	0.19	0.61	
*IL-10*T-819C	TT (n = 1149)	0.0301	0.0198	0.13	0.09	0.09	0.09	0.29	0.82
[rs1800871]	CT (n = 1165)	0.0419	0.0212	0.05		0.05	0.09	0.61	
	CC (n = 305)	−0.0059	0.0287	0.84		0.11	0.18	0.53	
IL-13 C-1111T	TT (n = 87)	−0.0294	0.0525	0.58	0.50	−0.75	0.59	0.20	0.41
[rs1800925]	TC (n = 785)	0.0421	0.0240	0.08		0.12	0.11	0.29	
	CC (n = 1747)	0.0277	0.0163	0.09		0.06	0.07	0.41	
TNF-α T-1031C	TT (n = 1857)	0.0318	0.0157	0.04	0.74	0.07	0.07	0.31	0.82
[rs1799964]	CT (n = 691)	0.0312	0.0262	0.23		0.04	0.11	0.74	
	CC (n = 71)	−0.0103	0.0522	0.84		−0.06	0.45	0.89	
TNF-α C-857T	CC (n = 1745)	0.0310	0.0158	0.05	0.74	0.07	0.07	0.30	0.67
[rs1799724]	CT (n = 784)	0.0348	0.0258	0.18		0.08	0.12	0.51	
	TT (n = 90)	−0.0132	0.0775	0.87		0.26	0.42	0.54	

HbA_{1c}, glycated hemoglobin; IL, interleukin; TNF, tumor necrosis factor; SE, standard error.
[a] β indicates regression coefficient of multiple regression between smoking (independent variable) and either HbA_{1c} or high-normal HbA_{1c} (dependent variables).
[b] Interaction with smoking status.
* $P < 0.05$.

polymorphism and cigarette smoking on a high-normal HbA_{1c} value (P interaction = 0.056).

3.3. Associations of the IL-1β T-31C polymorphism and cigarette smoking status with selected characteristics

Table 3 shows the univariate associations of the *IL-1β* T-31C polymorphism and smoking status with the six selected characteristics. The T allele of the *IL-1β* T-31C polymorphism was significantly and positively correlated with BMI and alcohol drinking. The current smokers had higher BMI values, higher energy intake and higher percentages of current drinkers and subjects with a first-degree family history of diabetes.

3.4. Associations between the IL-1β T-31C polymorphism and smoking status on the HbA_{1c} levels

Table 4 shows the adjusted mean of the HbA_{1c} level and ORs for a high-normal HbA_{1c} value according to the *IL-1β* T-31C polymorphism or smoking status. The *IL-1β* T-31C polymorphism was not significantly associated with the HbA_{1c} levels, whereas the smoking status was significantly and positively associated with the HbA_{1c} levels following adjustment for all confounding factors (model 2 for HbA_{1c}). The current heavy smokers had the highest OR for a high-normal HbA_{1c} value (1.30 [95% CI 0.90–1.89]) in comparison to never smokers, although the difference between these ORs did not reach statistical significance.

Table 3
Selected characteristics of the subjects by *IL-1β* (T–31C) genotypes or cigarette smoking status. The J-MICC Study 2005–2008.

Characteristics	*IL-1β* (T–31C)					Smoking status					
	CC (n = 584)	CT (n = 1274)	TT (n = 761)	r[a]	*P*[b]	Never (n = 1550)	Former (n = 620)	Current (n = 449)		r[a]	*P*[b]
								Moderate (<20 cigarettes/day)	Heavy (≥20 cigarettes/day)		
BMI (kg/m^2)[c]	23.1	23.1	23.4	0.05	<0.01*	22.9	23.7	22.6	23.8	0.10	<0.01*
Energy intake (kcal/day)	1737	1745	1766	0.03	0.08	1668	1889	1789	1871	0.28	<0.01*
Physical activity (MET·hours/day)[d]	13.1	13.0	13.0	0.00	0.91	13.1	12.3	13.3	13.9	−0.05	0.01*
Current smokers (%)	15.9	17.1	18.1	0.04	0.06	–					
Current drinkers (%)[e]	50.2	55.4	56.2	0.04	0.04*	41.1	76.2	70.2	70.6	0.39	<0.01*
First-degree family history of diabetes (%)	14.9	15.9	15.1	0.02	0.28	15.2	14.0	16.8	18.8	0.04	0.03*

Data values are expressed as the means. IL, interleukin; BMI, body mass index; MET, metabolic equivalent.
[a] Spearman's rank correlation coefficients between either *IL-1β* polymorphism or smoking status and six selected characteristics.
[b] *P* values for the Spearman's rank correlations.
[c] Based on 2618 subjects.
[d] Based on 2596 subjects.
[e] Based on 2577 subjects.
* $P < 0.05$.

Table 4
Adjusted means of BMI (kg/m^2), HbA_{1c} (%) or odds ratios for high-normal HbA_{1c} (≥5.7%) according to the *IL-1β* (T–31C) genotypes or cigarette smoking status. The J-MICC Study 2005–2008.

	IL-1β (T–31C)					Smoking status					
	CC	CT	TT	β[a]	*P* trend	Never	Former	Current		β[a]	*P* trend
								Moderate (<20 cigarettes/day)	Heavy (≥20 cigarettes/day)		
Adjusted means of BMI											
Model 1[b]	23.1 (22.9–23.4)	23.1 (22.9–23.2)	22.3 (23.1–23.5)	0.120	0.15	23.2 (23.0–23.4)	23.2 (22.9–23.5)	22.4 (21.9–22.9)	23.4 (23.0–23.8)	−0.019	0.79
Model 2[c]	23.1 (22.9–23.4)	23.1 (22.9–23.3)	23.3 (23.1–23.5)	0.080	0.34	23.2 (23.0–23.3)	23.3 (23.0–23.5)	22.5 (22.0–22.9)	23.4 (23.0–23.8)	−0.011	0.87
Adjusted means of HbA_{1c}											
Model 1[b]	5.49 (5.45–5.54)	5.50 (5.47–5.53)	5.53 (5.49–5.57)	0.022	0.16	5.50 (5.47–5.54)	5.50 (5.45–5.55)	5.45 (5.37–5.54)	5.58 (5.51–5.65)	0.017	0.20
Model 2[c]	5.50 (5.45–5.54)	5.50 (5.47–5.53)	5.53 (5.49–5.57)	0.016	0.29	5.49 (5.46–5.53)	5.50 (5.45–5.55)	5.47 (5.39–5.56)	5.61 (5.54–5.68)	0.030	0.02*
Adjusted odds ratios for high-normal HbA_{1c}											
Model 1[b]	1.00 (reference)	0.95 (0.76–1.20)	1.01 (0.78–1.30)	0.007	0.91	1.00 (reference)	1.17 (0.90–1.54)	0.83 (0.54–1.25)	1.08 (0.77–1.53)	−0.001	0.99
Model 2[c]	1.00 (reference)	0.95 (0.74–1.21)	0.98 (0.75–1.28)	−0.009	0.90	1.00 (reference)	1.24 (0.92–1.65)	1.04 (0.66–1.63)	1.30 (0.90–1.89)	0.070	0.24

Values are expressed as the adjusted means or odds ratios (95% confidence interval). BMI, body mass index; HbA_{1c}, glycated hemoglobin; IL, interleukin.
[a] Regression coefficients for the associations between either *IL-1β* (T–31C) polymorphism or cigarette smoking status and HbA_{1c} levels.
[b] Model 1: adjusted for sex and age.
[c] Model 2: adjusted for Model 1 and further adjusted for BMI (for the association between either IL-1β polymorphism or smoking status and HbA_{1c} levels), energy intake, physical activity, alcohol drinking, family history of diabetes mellitus, investigation site, smoking status (for the association of *IL-1β* polymorphism with HbA_{1c} levels) and *IL-1β* polymorphism (for the association of smoking with HbA_{1c} levels).
* $P < 0.05$.

3.5. Stratified analyses according to the IL-1β T-31C genotypes

As shown in Fig. 1A, the adjusted HbA_{1c} levels in the subjects carrying the C allele (CC or CT) were similar among the four different smoking status groups (CC: never 5.52 [95% CI 5.46–5.57] %, former 5.42 [5.32–5.52] %, current moderate 5.41 [5.24–5.58] %, current heavy 5.53 [5.39–5.67] %; CT: never 5.49 [5.45–5.53] %, former 5.51 [5.45–5.57] %, current moderate 5.49 [5.39–5.60] %, and current heavy 5.49 [5.40–5.58] %). In contrast, among the individuals carrying the TT genotype, the HbA_{1c} levels were significantly higher in heavy smokers (5.83 [5.67–5.99] %) than in all other smoking status groups (never 5.49 [5.41–5.56] %, former 5.54 [5.43–5.65] % and current moderate 5.50 [5.30–5.69] %). A similar pattern of results was observed regarding a high-normal HbA_{1c} value (Fig. 1B). The high-normal HbA_{1c} risk (adjusted OR) was significantly higher in the subjects carrying the TT genotype (never 1.00 [reference], former 1.21 [0.71–2.08], current moderate 1.35 [0.63–2.87] and current heavy 2.16 [1.14–4.10]), whereas the ORs were similar among the participants with the C allele (CC: never 1.00 [reference], former 0.85 [0.44–1.64], current moderate 0.39 [0.11–1.41] and current heavy 1.22 [0.57–2.64]; CT: never 1.00 [reference], former 1.46 [0.96–2.22], current moderate 1.18 [0.61–2.27] and current heavy 0.88 [0.48–1.62]).

3.6. Separate analyses according to sex

Since the smoking rate in females was low in the current subjects, additional subanalyses on the interaction between cigarette smoking and *IL-1β* T-31C polymorphism on HbA_{1c} values were performed for males and females. While interactions between the *IL-1β* T-31C polymorphism and cigarette smoking on the HbA_{1c} levels were not significant in females alone (HbA_{1c}: *P* interaction = 0.80; high-normal HbA_{1c}: *P* interaction = 0.65), significant interactions were observed when analyzed in males alone (HbA_{1c}: *P* interaction = 0.0016; high-normal HbA_{1c}: *P* interaction = 0.0796). As shown in Table 5, adjusted HbA_{1c} and high-normal HbA_{1c} values in male subjects showed a similar pattern to that for males and females combined.

4. Discussion

In the current study, we investigated whether the influence of cigarette smoking on the HbA_{1c} levels varied according to polymorphisms of inflammatory genes in a middle-aged Japanese population. Of the eight gene polymorphisms examined, only one statistically significant interaction was detected for the *IL-1β* T-31C polymorphism (*P* interaction < 0.0001). The association between cigarette smoking and the HbA_{1c} levels in subjects carrying C allele (CT or CC genotype) did not reach statistical significance, whereas the smoking status was positively associated with higher levels of HbA_{1c} in the individuals harboring the TT genotype (*P* trend = 0.001). A similar pattern of results was observed regarding the risk of high-normal HbA_{1c}. Therefore, the current results suggest that heavy smokers with the TT genotype of the *IL-1β* T-31C polymorphism may show a greater adverse effect of smoking on the HbA_{1c} levels among middle-aged Japanese subjects.

As mentioned in the introduction, the *IL-1β* gene expression response to cigarette smoking condensate was highest compared with several inflammation-related genes (Hellermann et al., 2002), therefore we presumed that its high reactivity to smoking could be a reason for the sole significant interaction detected in the current study. IL-1β is a major proinflammatory cytokine that is known to be produced from endothelial or epithelial cells and macrophages and plays a central role in the regulation of inflammatory responses (Banerjee and Saxena, 2012). IL-1β adversely affects peripheral insulin sensitivity; however, it is especially well known to be closely involved in the impairment of β-cells in pancreatic islets (Banerjee and Saxena, 2012). There are clinical reports showing that blocking the biological activity of IL-1β (via the administration of IL-1-receptor antagonist or IL-1β-specific antibody) improves both the HbA_{1c} level and insulin secretion, but not peripheral insulin sensitivity (Larsen et al., 2007; Donath and Shoelson, 2011; Sloan-Lancaster et al., 2013).

IL-1β mRNA is primarily synthesized as an inactive precursor IL-1β (called pro-IL-1β) and the immature protein is then digested by the proteolytic enzyme caspase 1 to produce a biologically active mature form of IL-1β (Dinarello, 2011). The *IL-1β* T-31C is a TATA-box polymorphism that profoundly affects DNA-protein interactions in vitro; the -31T allele has been shown to have a 5-fold enhanced binding activity with the transcription initiation factor by way of preserving TATA-box (El-Omar et al., 2000). Similarly, another study showed that the -31T allele is associated with a 10-fold increase in the transcriptional activity compared with the -31C allele (Chakravorty et al., 2006). Therefore, although the current subjects carrying the TT genotype might have had higher IL-1β production and may be susceptible to high HbA_{1c} levels, as shown in Table 4, an increase in the T allele alone was not

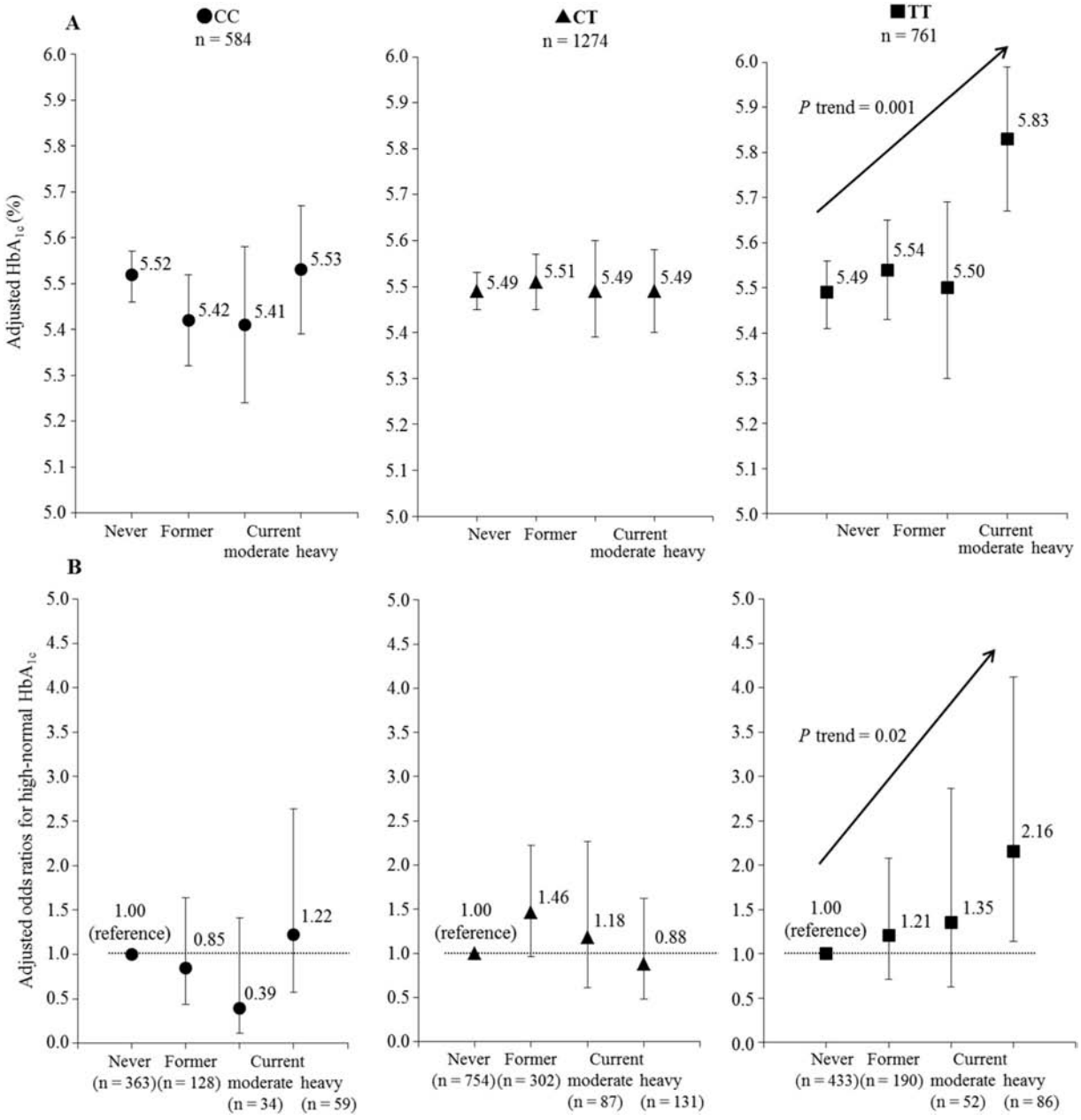

Fig. 1. Influence of cigarette smoking on the HbA_{1c} levels according to the *IL-1β* T-31C genotypes in the middle-aged Japanese subjects. Plots represent adjusted means of HbA_{1c} (A) or ORs for high-normal HbA_{1c} (B) and their 95% CIs. The J-MICC Study 2005–2008.

Table 5
Influence of cigarette smoking on the HbA_{1c} levels according to the *IL-1β* T-31C genotypes in male subjects. The J-MICC Study 2005–2008.

IL-1β (T–31C) genotypes	Smoking status				β[a]	*P* trend
	Never	Former	Current			
			Moderate (<20 cigarettes/day)	Heavy (≥20 cigarettes/day)		
Adjusted means of HbA_{1c}						
CC (n = 263)	5.55 (5.43–5.66)	5.47 (5.38–5.56)	5.50 (5.29–5.72)	5.52 (5.38–5.66)	−0.0053	0.86
CT (n = 612)	5.49 (5.42–5.56)	5.52 (5.46–5.57)	5.54 (5.42–5.66)	5.48 (5.40–5.57)	0.0001	1.00
TT (n = 399)	5.48 (5.31–5.65)	5.59 (5.45–5.72)	5.54 (5.23–5.85)	5.90 (5.69–6.10)	0.1279	<0.01*
Adjusted odds ratios for high-normal HbA_{1c}						
CC (n = 263)	1.00 (reference)	1.17 (0.53–2.58)	0.41 (0.08–2.22)	1.19 (0.45–3.18)	0.0068	0.97
CT (n = 612)	1.00 (reference)	1.53 (0.92–2.54)	1.80 (0.82–3.96)	0.95 (0.48–1.91)	0.0064	0.95
TT (n = 399)	1.00 (reference)	1.75 (0.94–3.28)	2.04 (0.79–5.32)	2.61 (1.23–5.55)	0.2982	0.013*

Values are expressed as the adjusted means or odds ratios (95% confidence interval). HbA_{1c}, glycated hemoglobin; IL, interleukin. Adjusted for sex, age, body mass index, energy intake, physical activity, alcohol drinking, family history of diabetes mellitus and investigation site.

[a] Regression coefficients for the associations between cigarette smoking status and HbA_{1c} levels.

* $P < 0.05$.

significantly associated with higher HbA_{1c} levels. This result does not support the concept that *IL-1β* plays an important role in controlling the blood glucose level (Spranger et al., 2003; Achyut et al., 2007; Banerjee and Saxena, 2012).

However, the current results showed that overlap of the *IL-1β* T-31C TT genotype and heavy smoking (≥20 cigarettes/day) may be unfavorably linked to higher HbA_{1c} levels, as shown in Fig. 1 and Table 5. There is a possible explanation for these results. It has been demonstrated in an animal study that cigarette smoke exposure increases the proteolytic caspase 1 activity as well as release of mature (biologically active) IL-1β (Eltom et al., 2011). Therefore, the current heavy smokers carrying the TT genotype might have demonstrated enhanced proteolytic cleavage of immature IL-1β by caspase 1, presumably activated by their heavy smoking, in pancreatic islets, in addition to preserving the increased synthesis of the IL-1β precursor due to the -31T genotype. Hence, we speculate that the coincidence of these two undesirable properties (i.e., the *IL-1β* T-31C TT genotype and heavy smoking) may lead to impaired insulin secretion, which can worsen the HbA_{1c} level.

The present result, namely that cigarette smoking was positively associated with higher HbA_{1c} levels only when adjusted for BMI (as shown in model 2 for the HbA_{1c} levels in Table 4), is consistent with a previous report indicating that heavy smoking has a protective effect regarding the future development of type 2 diabetes, mainly through the protection from obesity (Onat et al., 2007). It is well known that smoking has innumerable harmful effects on overall health in addition to a detrimental influence on the blood glucose level; smoking cessation should be highly encouraged among all current smokers, regardless of their distinct *IL-1β* T-31C genotype. However, achieving smoking cessation is quite cumbersome, assumingly because of the effects of nicotine dependence or addiction and/or insufficient motivation or drive to quit smoking. The current research provides evidence that smoking is especially harmful to individuals bearing the *IL-1β* T-31C TT genotype from the perspective of type 2 diabetes prevention, and this information may help individuals with the *IL-1β* T-31C TT genotype to avoid starting smoking or possibly consider smoking cessation. Therefore, the present findings are expected to contribute to the development of individualized smoking cessation programs based on a person's genetic background.

The current study is associated with several limitations. First, since we excluded participants currently using type 2 diabetes medications (n = 193) from the present analyses in order to avoid potential reversal of cause and effect, we were unable to assess the influence on the development of type 2 diabetes. Second, we have no replication data accompanying this study. Confirmation of the present findings by other researchers is expected in the future. Third, although we speculated that the higher levels of HbA_{1c} noted in the current heavy smokers having the *IL-1β* T-31C TT genotype may be attributed to insulin deficiency, we have no data on the circulating insulin concentrations. Additionally, the expression levels of the *IL-1β* gene in pancreatic β cells were not investigated, as performing a needle biopsy of the pancreas is impracticable in epidemiological studies. Finally, it should be noted that smoking may beneficially affect individuals harboring autoimmune activation (Onat and Can, 2014; Altay et al., 2015; Rasouli et al., 2013), however, we had pertinent no data to identify such individuals in the current population.

5. Conclusion

We found an interaction between the *IL-1β* T-31C polymorphism and the cigarette smoking status regarding the HbA_{1c} levels, as heavy smokers harboring the TT genotype of *IL-1β* T-31C may exhibit a greater adverse effect of cigarette smoking on the HbA_{1c} levels. The smoking status did not interact with any other inflammation-related polymorphisms except IL-1β T-31C. Further studies are needed to confirm the current results in different subject populations and understand the precise mechanisms underlying this interaction.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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