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

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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

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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