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Association of IL-4 receptor gene polymorphisms with high density lipoprotein cholesterol

Yih-Hsin Chang [a], Chien-Ning Huang [b,c], Ming-Yuh Shiau [d,*]

[a] Department of Biotechnology and Laboratory Science in Medicine, National Yang-Ming University, Taipei 112, Taiwan
[b] Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung 402, Taiwan
[c] Institute of Medicine, Chung Shan Medical University, Taichung 402, Taiwan
[d] Hungkuang University, Taichung 433, Taiwan

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ABSTRACT

The aim of this study is to investigate the correlation between E400A polymorphisms of interleukin-4 receptor α chain (IL-4Rα) and lipid metabolism. Genomic DNA from 121 type 2 diabetes mellitus (T2DM) patients and 113 non-diabetic, non-obese control study subjects were extracted, and their *IL-4Rα* E400A polymorphisms were analyzed by PCR-RFLP. The correlation between *IL-4Rα* E400A genotypes and study subjects' lipid profile was then examined. Significant associations of the *IL-4Rα* E400A genotypes and high density lipoprotein-cholesterol (HDL-C) levels among control individuals ($p = 0.007$), as well as among the T2DM patients ($p = 0.029$), were observed. Significant correlations between *IL-4Rα* E400A genotypes with blood pressure, as well as with blood urea nitrogen, were also observed in control subjects. Our results reveal that IL-4Rα may play certain roles in the lipid metabolism of Taiwanese population and suggest a novel link between lipid metabolism and the cytokine receptor.
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1. Introduction

Atherosclerosis is an inflammatory-fibrotic response of accumulating cholesterol in the artery wall. In hypercholesterolemia, the proinflammatory compounds produced by the oxidation of low density lipoproteins (LDL) in the arterial intima will result in activation of inflammatory responses, such as secretion of various cytokines and expression of adhesion molecules [1–7]. In mice model, it was reported that severe hypercholesterolemia is associated with a switch from type 1 T helper cell (Th1) to Th2 immune response, with increasing numbers of interleukin-4 - (IL-4) producing Th2 cells in the spleen and the appearance of IL-4 transcripts in the atherosclerotic lesion [8]. IL-4 mRNA can also be detected in atherosclerotic lesions from human [9]. Therefore, the local expression of IL-4 in atherosclerosis lesions is suggested to be involved in the atherogenic process.

Th2 cytokine IL-4 is a pleiotropic cytokine that inhibits the secretion of the pro-inflammatory cytokines from macrophages and plays crucial roles in atopic disorders [10–12]. The effects of IL-4 on Th1/Th2 balance and on other immune phenotypes are mediated by binding to the IL-4 receptor (IL-4R) [13]. The heterodimeric IL-4R protein consists of a 140 kDa high-affinity α subunit (IL-4Rα) encoded by the IL-4R locus (MIM 147781) on chromosome 16p11.2–12.1 [14,15], and a common γ chain shared by several interleukin receptors [16]. By binding to IL-4R, IL-4 regulates various cellular responses, including proliferation and survival of lymphocytes, immunoglobulin isotype switching to IgE, Th2 lineage commitment of CD4+ T cells and expression of class II major histocompatibility complex and FcεRII (CD23) [17].

Several single nucleotide polymorphisms (SNPs) have been identified in the IL-4Rα gene, among which some SNPs result in amino acid exchanges in the IL-4Rα chain and some can influence signal transduction as well as the expression of IL-4R [18–22]. Thus, SNPs within the IL-4Rα locus, as those within the genes encoding the ligand IL-4, might represent a set of candidate gene polymorphisms involved in the regulation of immune responses and susceptibility of diseases, including atherosclerosis. Therefore, it is tempting to identify whether the IL-4Rα gene polymorphisms would contribute to lipid metabolism which subsequently affects the atherogenic pathogenesis.

In this context, the present study aimed at investigating if the IL-4Rα gene is associated with lipid profile in Taiwanese population. Among the identified *IL-4Rα* SNPs, the variant alleles at rs1805011 (E400A), rs1805012 (C431R), and rs1801275 (Q576R)

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CRE, creatinine; HDL-C, high density lipoprotein-cholesterol; IL-4, interleukin-4; IL-4R, IL-4 receptor; IL-4Rα, interleukin-4 receptor α chain; LDL, low density lipoproteins; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphisms; Th1, type 1 T helper cell; T2DM, type 2 diabetes mellitus.

* Corresponding author. Tel.: +886 4 26318652x7090; fax: +886 4 26522280.
E-mail address: ming@sunrise.hk.edu.tw (M.-Y. Shiau).

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are reported to be negatively associated with T1DM, another diabetic type with abnormalities in lipid metabolism [18,23,24]. The SNPs I75V, S478P, and Q576R are absent in Chinese population while E400A is frequently observed in Japanese, a population which is ethnically much related to Taiwanese, compared with Caucasians [25]. To inspect our hypothesis, putative association between the E400A of IL-4Rα gene and lipid profile among non-diabetic, non-obese healthy individuals and patients with type 2 diabetic mellitus (T2DM) was examined. Significant associations between the IL-4Rα E400A genotypes and high density lipoprotein-cholesterol (HDL-C) levels were observed. Our results reveal that IL-4Rα E400A SNPs may play certain roles in lipid metabolism of Taiwanese population and suggest a novel link between lipid metabolism and the cytokine receptor.

2. Materials and methods

2.1. Study subjects

Fasting venous blood samples from 234 study subjects, including 113 non-diabetic, non-obese control individuals and 121 obese T2DM patients were collected. The information of body height, weight, body mass index (BMI), age, fasting blood sugar, renal function index (creatinine [CRE] and blood urea nitrogen [BUN]), and lipid profile (listed in Table 1), were collected for further statistical analysis. Written consents were obtained from all the study subjects after the nature of the procedure was explained. The study was carried out according to the principles of the Declaration of Helsinki.

2.2. Analysis of IL-4Rα gene polymorphisms

Genomic DNA was extracted from peripheral blood mononuclear cells. Aliquot of the genomic DNA (50–100 ng) was used for amplifying the DNA fragments containing target sequences by polymerase chain reaction (PCR). Generally, DNA amplification was performed in a 20 μL volume containing 10 pmol of each primer (5′-TGGAGATCAGCAAGACAGTC-3′ and 5′-GGTCCAGGAACAGGCTC TCT-3′), 4.5 mM $MgCl_2$, 0.25 mM of each dNTP, 1 U Taq polymerase, and 1.5 mM buffer with a 95 °C initial incubation for 5 min, followed by 30 amplification cycles (94 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s) and a final extension for 10 min at 72 °C. Polymorphisms of the amplified DNA products were examined by restriction fragment length polymorphism (RFLP) with Aci *I* digestion.

2.3. Statistical analysis

Data analysis started with descriptive statistics, including mean and standard deviation for continuous variables, and frequency for categorical variables. If necessary, natural logarithm transformation was used to enhance normality for blood biochemistry parameters with skewed distribution. Student's *t* test was applied for comparisons of age, BMI, and each of the blood biochemistry parameters between subjects with different genotype. An alpha level of 0.05 was used for all statistical tests.

3. Results

3.1. Distribution of IL-4Rα gene polymorphisms among study subjects

Our study aimed at investigating the distribution of IL-4Rα gene E400A SNPs among two groups of study subjects, including non-obese control individuals (with BMI 24.80 ± 4.60) and type 2 diabetic patients (with BMI 25.09 ± 3.11), to test the possible association between IL-4Rα genetic polymorphisms and lipid metabolism. Demographic data and clinical biochemical parameters of the patients were listed in Table 1. Except for diastolic pressure, circulatory creatinine and cholesterol levels, significant differences were observed among various clinical parameters between control and diabetic subjects.

Ninety-seven (85.8%) and 16 (14.2%) control individuals carried A/A and C/C genotype at E400A position of IL-4Rα gene, respectively, while 106 (87.6%) and 15 (12.4%) diabetic patients have A/A and C/C genotype, respectively (Table 2). No significant difference in distribution of IL-4Rα E400A genotypes between T2DM patients and control subjects was observed ($p = 0.831$). The genotype results suggested that the IL-4Rα polymorphisms were not associated with T2DM.

3.2. Association of IL-4Rα gene polymorphisms with clinical parameters of control subjects (Table 3)

Association between IL-4Rα E400A gene polymorphisms and study subjects' biochemical data was further examined to explore the possible role of this SNP and subjects' lipid profile. Trends toward significant difference of systolic pressure ($p = 0.043$) and diastolic pressure ($p = 0.049$) were observed between control subjects with A/A and C/C genotypes. Notably, significant differences in levels of BUN ($p = 0.039$) and high density lipoprotein-cholesterol (HDL-C; $p = 0.007$) with IL-4Rα E400A genotypes were also observed among control subjects. No significant association of other biochemical parameters (including CRE, cholesterol, and triglycerides) was found when control subjects were stratified by their genotypes.

3.3. Association of IL-4Rα gene polymorphisms with clinical parameters of T2DM subjects (Table 4)

When the putative association between IL-4Rα E400A gene polymorphisms and biochemical data was investigated among

Table 1
Demographic and biochemical data of study subjects in this study.

	Control $n = 113$	T2DM $n = 121$	p[b]
Male/female	62/51	69/52	NS
Age (y/o)	58.17 ± 10.70	59.84 ± 10.57	NS
BMI (kg/m^2)	24.80 ± 4.60	25.09 ± 3.11	0.014
Fasting glucose (70–110 mg/dL)[a]	94.92 ± 6.86	169.00 ± 52.32	<0.001
Systolic pressure (120–140 mm Hg)[a]	124.92 ± 19.39	131.79 ± 18.66	<0.001
Diastolic pressure (70–90 mm Hg)[a]	78.48 ± 11.50	77.96 ± 11.15	NS
Blood urea nitrogen (7–21 mg/dL)[a]	15.64 ± 4.27	16.54 ± 5.47	0.025
Creatinine(0.6–1.4 mg/dL)[a]	1.10 ± 0.35	1.07 ± 0.31	NS
Cholesterol (125–240 mg/dL)[a]	196.31 ± 36.85	200.43 ± 45.49	NS
HDL-C (>35 mg/dL)[a]	62.12 ± 13.88	48.81 ± 14.94	<0.001
TC/HDL-C	4.30 ± 0.90	4.40 ± 1.30	<0.001
Triglycerides (20–200 mg/dL)[a]	135.97 ± 107.08	172.45 ± 156.58	0.004

[a] Numbers in parenthesis indicated the normal reference range of each biochemical test.
[b] NS indicated non-significant.

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