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学 位 論 文

**(CCTTT)_n repeat polymorphism in the *NOS2* gene
promoter is associated with atopy**

NOS2 遺伝子プロモーター領域の CCTTT 繰り返し多型とアトピーとの関連

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**(CCTTT)_n repeat polymorphism in the *NOS2* gene
promoter is associated with atopy**

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ABSTRACT

Background: Several studies have shown that nitric oxide (NO) plays a role in the regulation of the T helper1 (Th1)/Th2 balance, indicating the potential for NO to contribute to the development of atopy and several other allergic diseases including bronchial asthma. Nitric oxide synthase 2 (NOS2) is critically involved in the synthesis of NO during several inflammatory states, and the gene encoding NOS2 is located at chromosome 17q11.2-q12, where two genome scans have identified a candidate locus for atopy and asthma.

Objective: The 14-repeat allele of (CCTTT)_n repeat polymorphism in the NOS2 promoter region is a powerful enhancer of promoter activity in reporter constructs *in vitro*. We tested whether this potentially functional allele in the NOS2 gene influences the development of atopy and asthma.

Methods: We studied a total of 497 unrelated Japanese subjects (141 non-atopic healthy controls, 102 atopic healthy controls, 56 non-atopic asthmatics, and 198 atopic asthmatics). The odds ratio was calculated for atopy and asthma in carriers of the 14-repeat allele using logistic regression models. Atopy was defined as having a positive specific IgE level to at least one of 10 common inhaled allergens.

Results: The 14-repeat allele was inversely associated with atopy (OR=0.42, p<0.01). The

association remained significant when the model was controlled for asthmatic status (OR=0.36, $p<0.01$). This allele, however, was neither associated with the development of asthma nor with total serum IgE levels.

Conclusion: Our findings suggest that the (CCTTT)_n repeat polymorphism in the promoter of the *NOS2* gene that affects the promoter activity is a risk factor for the development of atopy, and this genetic effect seems independent of asthma.

Key words: Atopy, asthma, nitric oxide synthase 2 (NOS2)

INTRODUCTION

Nitric oxide (NO) is a short-lived molecule that plays several important pathophysiological roles in the development of various diseases. Nitric oxide synthase 2 (NOS2) is induced in a variety of cell types by proinflammatory cytokines, including IL-1 β , TNF- α , IFN- γ , or microbial products such as LPSs^{1,2}, and is critically involved in the synthesis of NO during infection and other inflammatory states. Genetic polymorphisms at the *NOS2* gene are associated with susceptibility to malaria and parasitic diseases^{3,4}. Several recent studies have also indicated that NO is not only a potent cytotoxic and antimicrobial agent, but also exhibits significant immunoregulatory activity, regulating the T helper1 (Th1)/Th2 balance particularly⁵⁻¹⁰.

The *NOS2* gene lies within the C-C chemokine cluster region, on chromosome 17q11.2-q12, where a linkage with atopy and asthma has been reported^{11,12}. Within the 5'-flanking DNA, a (CCTTT)_n repeat sequence is located ~2.5 kb upstream of the main TATA-directed transcription initiation site¹³. The 14-repeat allele is linked to increased luciferase activity with *in vitro* reporter constructs¹⁴, and this allele confers selective advantages in diabetic individuals by preventing microvascular complications of diabetes^{14,15}. Accordingly, we postulated that polymorphisms in the *NOS2* gene influence the development of atopy and asthma, and examined the prevalence of this 14-repeat allele in

unrelated Japanese healthy controls and asthmatic subjects.

METHODS

Study Subjects

Unrelated Japanese subjects were recruited to this study (141 non-atopic healthy controls, 102 atopic healthy controls, 56 non-atopic asthmatics, and 198 atopic asthmatics; Table I). Individuals who visited our clinic for annual, routine physical examinations were recruited as healthy controls if they had no history of bronchial asthma or any other allergic disease. Asthmatic subjects were recruited from the pulmonary clinic at the First Department of Medicine, Hokkaido University Hospital. Asthma was defined on the basis of recurrent episodes of at least two of three symptoms (cough, wheeze, or dyspnea) that are associated with a demonstrable reversible airflow limitation, and/or increased airway responsiveness as described previously ¹⁶. Atopy was defined as having a positive specific IgE level (IgE CAP RAST equal to or more than 0.35 U_A/ml to at least one of 10 common inhaled allergens, including *Dermatophagoides farinae* [*Der f*], grass pollens, animal danders, and moulds). Total serum IgE levels of all participants were also measured using a radio-immunosorbent test (IgE RIST).

This study was approved by the Ethics Committee of Hokkaido University School of Medicine and informed written consent was obtained from each subject.

Analysis of a (CCTTT)_n repeat polymorphism of the *NOS2* promoter region

Laboratory staff blinded to clinical data performed genotyping. Genomic DNA was amplified by PCR using a FAM-labeled sense primer (5'-ACC CCT GGA AGC CTA CAA CTG CAT-3') and an anti-sense primer (5'-GCC ACT GCA CCC TAG CCT GTC TCA-3') as described previously ¹³. The PCR products were separated by electrophoresis through a POP-4™ gel using an ABI 310 (PE Applied Biosystems, Foster City, CA) with TAMURA-500™ as the internal size standard. Allele sizes were calculated using the Genescan Analysis™ computer program (PE Applied Biosystems).

Statistical analysis

The Hardy-Weinberg equilibrium was examined using the HWE program 1.05 in the LINKUTIL package ¹⁷. Pearson chi-square analysis compared the distribution of the 14-repeat allele and genotype between non-atopic and atopic subjects, and between healthy controls and asthmatics. We then used logistic regression models to calculate odds ratios (and 95% confidence intervals) of atopy associated with the 14-repeat allele. To control for potential confounding, we adjusted for age (as a continuous variable), sex (male or female), and smoking status (never smoked, past smoking, or current smoking) in the multivariate models (Stat View 5.0, 1998 SAS Institute Inc.). Genetic influence of the 14-repeat allele

on the development of atopy was also examined controlling for asthmatic status (asthma or healthy controls) in addition to age, sex and smoking status.

We used an ANOVA model and compared total serum IgE levels according to the 14-repeat genotypes (the 14-repeat allele carriers vs. non-carriers). In this analysis, we adjusted for asthmatic status and atopic status (atopic or non-atopic) in addition to age, sex and smoking status.

RESULTS

Characteristics of the 197 non-atopic (141 non-asthmatic, 56 asthmatic) and 300 atopic (102 non-asthmatic, 198 asthmatic) subjects are presented in Table I. The mean age was highest for non-atopic asthmatics, and females also predominated in this group. Atopic subjects had higher total serum IgE levels than non-atopic subjects (unpaired *t*-test, $p<0.01$) both in healthy controls and asthmatic subjects. In addition, asthmatic subjects had higher total serum IgE levels than healthy controls (unpaired *t*-test, $p<0.01$) both in non-atopic and atopic subjects.

A pentanucleotide repeat in the promoter region of the human *NOS2* gene revealed a total of 14 alleles in 994 chromosomes (allele sizes varied from 176bp [8 repeats] to 241bp [21 repeats]). The (CCTTT)_n genotype frequencies did not deviate from the expected value by Hardy-Weinberg equilibrium. The overall distribution of the allele frequencies according to atopic status is shown in the Figure. The genotype and allele distributions for the 14-repeat allele of the 197 non-atopic subjects differed significantly from those of the 300 atopic subjects (genotype; chi-square=6.13, $p=0.013$, allele; chi-square=7.48, $p=0.0063$, Table II A). An odds ratio calculated for atopy in carriers of the 14-repeat allele compared with non-carriers was 0.42 (95%CI [0.23-0.79]; $p=0.0065$, Table III A). The odds ratio remained significant when the model was also adjusted for asthmatic

status (OR=0.36, 95%CI [0.18-0.71], $p=0.0032$; Table III B). This repeat polymorphism, however, was not associated with asthma (Table II B). The mean adjusted total serum IgE level in the 14-repeat carriers (2.20 [SD 0.55]) was not different from those in non-carriers (2.13 [0.54]).

DISCUSSION

In the present study, we identified a significantly increased prevalence of the 14-repeat allele of the (CCTTT)_n repeat at the *NOS2* promoter region in non-atopic subjects. The mechanism by which the pentanucleotide repeat polymorphism, or a related regulatory polymorphism in the *NOS2* gene promoter region, influences the development of atopy is as yet unclear. Significant associations between the 14-repeat allele and the absence of the diabetic retinopathy or nephropathy, especially in insulin-dependent (type 1) diabetic patients, have been reported ^{14, 15}. It is suggested that clinically distinct inflammatory immune diseases including insulin-dependent diabetes mellitus and atopy are controlled by a common set of susceptibility genes ¹⁸. Therefore, the 14-repeat allele is potentially a susceptibility or disease-modifying allele of inflammatory immune diseases such as atopy and diabetes mellitus.. Polypyrimidine/polypurine repeats in the promoter region may affect transcription by forming the unusual triplex DNA structure ¹⁹. The 14 repeat allele also displayed a greater increase in reporter gene expression under both conditions of normal and high glucose concentrations ¹⁴, suggesting that, in individuals possessing this potentially functional allele, *NOS2* may be expressed to a greater extent in response to exogenous stimuli including several pathogens such as viruses or bacteria, leading to exaggerated NO production. Alternatively, a true susceptibility allele at the

NOS2 gene or another nearby gene that is in linkage disequilibrium with the 14-repeat allele may explain our finding of a significant association between atopy and the 14-repeat allele.

Recently NO has emerged as an immunoregulatory molecule that is involved in the regulation of Th1/Th2 subset balance ⁵⁻¹⁰. NO has an inhibitory effect on T cell activation, and cytokine production in Th2 cells is more susceptible to this effect than that in Th1 cells ⁷. At the inductive phase of Th1 cells, NO even showed an enhancing effect on the induction and differentiation of Th1 cells, with little or no effect on fully committed T cells ⁹. In the first few years of life, children are considered to be highly susceptible to immunomodulation with long-lasting effects ²⁰ and the very first period of life is indeed important in the establishment of atopic status ²¹. Several findings also indicate that childhood exposure to infectious agents, including mycobacteria, prevent allergic sensitization through the preferential induction of Th1-type cytokines ^{22,23}. Taken together, individuals carrying the 14-repeat allele may have higher induction of NO by several infectious agents in their early childhood, acquiring a Th1-polarized immune system, and have decreased susceptibility to allergic sensitization when they are subsequently exposed to common environmental allergens.

Conversely, some other studies reported that *NOS2* deficient mice developed an

enhanced Th1 response following infections and antigenic stimulation^{6,8}, suggesting that NO modulates the Th1/Th2 balance by favoring Th2 responses. Indeed, a significant correlation was found between exhaled NO levels in adults with established asthma and atopy, measured by total serum IgE levels and a positive skin-prick test²⁴. A possible explanation for the discrepancy between this findings and ours is that NO has different selective roles in the regulation of the Th1/Th2 balance depending upon the types of target cells involved, states of airway inflammation or the concentration of NO locally released in the airways⁸⁻¹⁰.

A recent longitudinal prospective study suggested that asthmatic subjects have increased susceptibility to have higher IgE responsiveness²⁵. Asthmatic subjects also have increased levels of NO and NOS2 expression in their airways²⁶. Given the possibility that asthmatic status modulates the genetic manifestation of the 14-repeat allele, we also calculated an odds ratio for the development of atopy by controlling for asthmatic status in addition to age, sex and smoking status, and found that the genetic effect of the 14-repeat allele on atopy was independent of asthma. Our study also failed to show an association between asthma and the NOS2 promoter polymorphism. Moreover, murine models with targeted deletions of each NOS gene have shown that NOS1 but not NOS2 is important for the development of the airway hyperresponsiveness^{27,28}. Collectively, it appears that the

14-repeat allele at the *NOS2* gene is one of the distinct genetic factors that affect the development of atopy, but not asthma ²⁹.

In the *NOS2* gene, a bi-allelic tetranucleotide repeat sequence within the 5'-flanking region at ~750bp from the transcription initiation site in promoter region has also been identified ³⁰, although the functional consequence of the polymorphism is unclear at this time. Gao and colleagues found that this bi-allelic polymorphism is equally distributed between asthmatics and healthy controls, and between atopic and non-atopic individuals ³¹. We did not, however, detect polymorphisms at this locus in 400 chromosomes from the 100 Japanese asthmatics and 100 Japanese healthy controls (all subjects had an identical genotype) in our study population.

In conclusion, a potentially functional 14-repeat allele at the *NOS2* gene promoter region is inversely associated with atopy. This result tends to support the notion that enhanced expression of *NOS2* modulates the Th1/Th2 balance towards Th1 responses *in vivo*, which might result in inhibition of allergic sensitization when exposed to common allergens. The *NOS2* gene lies within the C-C chemokine cluster region on chromosome 17q11.2-q12, ^{11, 12} and the 14-repeat allele may contribute to a significant linkage between this region and atopy. Confirmation of our preliminary finding using a second, larger and independent population sample, and a detailed functional analysis would provide a better

understanding of the genetic significance of the 14-repeat allele and the protective effect of NO on the development of atopy.

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TABLE 1 . Demographic characteristics of study participants according to the 14-repeat genotype

			No. of subjects	Age yr	Sex f/m	Current smoker No. (%)	Total IgE log IU/ml
Non-atopic subjects							
Healthy Control			141	44.4 ± 10.7	61/80	54 (38.3%)	1.57 ± 0.55
14-repeat	(+)		17	43.4 ± 11.3	8/9	5 (29.4%)	1.82 ± 0.28
14-repeat	(-)		124	44.6 ± 10.7	53/71	49 (39.5%)	1.53 ± 0.57
Asthma			56	55.4 ± 11.2	40/16	8 (14.3%)	1.90 ± 0.55
14-repeat	(+)		10	55.4 ± 11.2	7/3	0 (0 %)	1.86 ± 0.38
14-repeat	(-)		46	55.3 ± 11.3	33/13	8 (17.4%)	1.91 ± 0.58
Atopic subjects							
Healthy Control			102	42.3 ± 11.7	40/62	38 (37.3%)	2.18 ± 0.54
14-repeat	(+)		6	34.2 ± 12.2	3/3	2 (33.3%)	1.87 ± 0.63
14-repeat	(-)		96	42.8 ± 10.7	37/59	36 (37.5%)	2.20 ± 0.53
Asthma			198	40.9 ± 16.6	100/98	56 (28.3%)	2.58 ± 0.56
14-repeat	(+)		15	35.1 ± 14.4	8/7	7 (46.7%)	2.64 ± 0.70
14-repeat	(-)		183	41.1 ± 16.7	92/91	49 (26.8%)	2.57 ± 0.55

Data are mean ± SD

TABLE II. Genotype and allele frequencies for the 14-repeat allele

(A)

	Non-atopic subjects	Atopic subjects
Genotype, No. of subject (%)		
14-repeat/ 14-repeat	3 (1.5)	1 (0.3)
14-repeat/ others	24 (12.2)	20 (6.7)
others/ others	170 (86.3)	279 (93.0)
Allele, No. of subjects (%)		
14-repeat	30 (7.6)	22 (3.7)
others	364 (92.4)	578 (96.3)

(B)

	Healthy Controls	Asthmatic subjects
Genotype, No. of subject (%)		
14-repeat/ 14-repeat	1 (0.4)	3 (1.2)
14-repeat/ others	22 (9.1)	22 (8.7)
others/ others	220 (90.5)	229 (90.1)
Allele, No. of subjects (%)		
14-repeat	24 (4.9)	28 (5.5)
others	462 (95.1)	480 (94.5)

(A) Significant differences in genotype and allele distributions for the 14-repeat allele were observed

(genotype; chi-square=6.13, p=0.013, allele; chi-square=7.48, p=0.0063) between non-atopic and atopic subjects.

(B) No significant differences were observed (genotype; chi-square=0.02, p=0.89, allele; chi-square=0.17, p=0.68)

between healthy control and asthmatic subjects.

TABLE III. Logistic regression models for the development of atopy*

(A)				(B)			
Variables	OR	95%CI	p Value	Variables	OR	95% CI	p Value
Age	0.97	0.96-0.98	<0.0001	Age	0.96	0.94-0.97	<0.0001
Sex	1.22	0.82-1.79	0.33	Sex	1.57	1.02-2.42	0.040
Smoking status	0.79	0.52-1.20	0.27	Smoking status	1.02	0.64-1.67	0.92
14-repeat allele	0.42	0.23-0.79	0.0065	14-repeat allele	0.36	0.18-0.71	0.0032
				Asthmatic status	6.61	4.23-10.3	<0.0001

Definition of abbreviation OR : odds ratio, CI : confidence interval

* The odds ratio was calculated for the development of atopy in the 14-repeat allele carriers compared with non-carriers.

In a model (B), the analysis was adjusted for asthmatic status (asthmatic or healthy control) in addition to adjustment for age, sex, smoking status (never smoked, past smoking or current smoking), and the 14-repeat genotypes (carriers or non-carriers).

FIGURE

