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IL3 SNP rs40401 variant is a risk factor for rhinoconjunctivitis in Japanese women: The Kyushu Okinawa Maternal and Child Health Study

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ABSTRACT

Background: No studies have investigated the relationship between *IL3* single nucleotide polymorphism (SNP) rs40401 and allergic rhinitis. We performed a case-control study to examine this issue and to assess interactions between the SNP and smoking or older siblings in young adult Japanese women.
Methods: Included were 393 women who met the criteria of the International Study of Asthma and Allergies in Childhood (ISAAC) for rhinoconjunctivitis. Controls were 767 women without rhinoconjunctivitis according to the ISAAC criteria who had not been diagnosed with allergic rhinitis by a doctor.
Results: Compared with women with the TT genotype of SNP rs40401, those with the CC genotype had a significantly increased risk of rhinoconjunctivitis: the adjusted OR was 1.52 (95% CI: 1.05-2.19). This positive relationship was significant under the additive model: the adjusted OR was 1.23 (95% CI: 1.02-1.47). The positive association fell just short of the significance level under the dominant or recessive model. There was no significant interaction between SNP rs40401 and smoking with respect to rhinoconjunctivitis. Compared with subjects with the TT or TC genotype of *IL3* SNP rs40401 who had one or more older siblings, those with the CC genotype who had no older siblings had a 2.33-fold increased risk of rhinoconjunctivitis; nevertheless, the interaction was not significant.
Conclusion: This is the first study to show a significant positive association between *IL3* SNP rs40401 variant and the risk of rhinoconjunctivitis. We could not find evidence for interactions between SNP rs40401 and smoking or older siblings affecting rhinoconjunctivitis.

1. Introduction

Allergic rhinitis is the most common allergic disorder in Japan. In a nationwide study of 22,819 Japanese aged 20–79 years, the age-adjusted prevalence of rhinitis as defined according to the European Community Respiratory Health Survey questionnaire was 35.1% in men and 39.3% in women [1]. A complex interaction among genetic and environmental factors is likely to be involved in the development of allergic rhinitis.

Interleukin-3 (IL-3) is a cytokine that regulates the production and function of cells of the hematopoietic and immune systems and is expressed mainly by activated T lymphocytes and mast cells [2]. IL-3 also stimulates pro-inflammatory reactions from immune cells such as the release of histamine, IL-4, and IL-13 from basophils and eosinophil degranulation [2].

The *IL3* gene is located on chromosome 5q23–5q31. The *IL3* single nucleotide polymorphism (SNP) rs40401 variant in exon 1 arises due to a thymine-to-cytosine transversion at position +79, resulting in an amino acid change from serine to proline at residue 27 when including the leader sequence, or at residue 8 in the secreted form of human IL-3. To our knowledge, only four investigations have examined the relationship between *IL3* SNP rs40401 and asthma, and these have produced inconsistent results [3–6]. No studies have investigated the relationship between SNP rs40401 and allergic rhinitis or the gene-environment interactions associated with SNP rs40401 and allergic disorders.

Here, we conducted a case-control study of the relationship between *IL3* SNP rs40401 and rhinoconjunctivitis in a population of young adult Japanese women using data from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS). We also investigated the possibility of an interaction between *IL3* SNP rs40401 and smoking or older siblings.

2. Subjects and methods

2.1. Study population

The KOMCHS is a prospective prebirth cohort study. Details of the baseline survey of the KOMCHS have been described elsewhere [7]. Eligible women were those who became pregnant while living in one of seven prefectures on Kyushu Island in southern Japan,

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with a total population of approximately 13.26 million, or in Okinawa Prefecture, an island chain in the southwest of Japan, with a total population of nearly 1.37 million. Between April 2007 and March 2008, we requested that 423 obstetric hospitals in the above-mentioned eight prefectures provide as many pregnant women as possible with a set of leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed and stamped return envelope. Pregnant women who were willing to participate in the study returned the application form to the data management center. In total, 1757 pregnant women between the 5th and 39th weeks of pregnancy gave their full informed consent in writing to participate in the KOMCHS and completed the baseline survey. Around 4 months after delivery, 1492 women gave informed consent to genotyping. The ethics committee of the Faculty of Medicine, Fukuoka University approved the KOMCHS.

2.2. Selection of cases and control subjects

In accordance with the questions in the International Study of Asthma and Allergies in Childhood (ISAAC) [8], the presence of rhinoconjunctivitis was defined as a positive response to the following two questions: 'In the last 12 months, have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or flu?' and 'In the last 12 months, has this nose problem been accompanied by itchy–watery eyes?' Among the 1492 women whose DNA samples were available, 393 cases of rhinoconjunctivitis were identified. Among the 1099 remaining women who were eligible to serve as control subjects, 331 women were excluded who were not considered to have rhinoconjunctivitis as defined by the ISAAC criteria but who had answered 'yes' to the question: 'Have you ever been diagnosed by a physician as having allergic rhinitis?' One woman was also excluded due to incomplete data on smoking. Thus data from 393 cases and 767 control subjects were ultimately available for analysis.

2.3. DNA extraction and genotyping

Genomic DNA from buccal specimens collected with BuccalAmp swabs (Epicenter BioTechnologies, Madison, WI, USA) was extracted using a QIAmp DNA mini kit (Qiagen, Inc., Valencia, CA, USA). Genotyping of *IL*3 SNP rs40401 was performed using a TaqMan SNP Genotyping Assay on the StepOnePlus machine (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's instructions.

2.4. Statistical analysis

We tested agreement with Hardy–Weinberg equilibrium using the chi-square test. Logistic regression analysis was applied to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) of rhinoconjunctivitis in relation to *IL*3 SNP rs40401, with the reference category being the homozygote of the ancestral allele based on the National Center for Biotechnology Information SNP database. Multiple logistic regression analysis was used to adjust for age, region of residence, presence of older siblings, smoking, and education. The statistical power calculation was performed using QUANTO version 1.2 [9]. We examined multiplicative and additive interactions between *IL*3 SNP rs40401 and smoking or older siblings with regard to the risk of rhinoconjunctivitis. Multiplicative interaction was estimated by introducing a multiplicative term into a multiple logistic regression model. Three measures for the additive interaction were calculated using the Excel sheet provided by Andersson et al. [10]: (1) relative excess risk due to interaction (RERI), (2) attributable proportion due to interaction (AP), and (3) synergy index (S). RERI is the excess risk due to an interaction relative to the risk without exposure. AP refers to the attributable proportion of disease among individuals exposed to both factors that is due to the factors' interaction. *S* is the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without an interaction. RERI = 0, AP = 0, or $S = 1$ means no interaction or strict additivity; RERI > 0, AP > 0, or $S > 1$ means a positive interaction or more than additivity; RERI < 0, AP < 0, or $S < 1$ means a negative interaction or less than additivity [11]. If any of the null values (0 in RERI and AP or 1 in *S*) falls outside the 95% CI of its respective measurement, then the additive interaction is considered statistically significant. Except for the statistical power calculation, all statistical analyses were performed using STATA/SE software version 12.0 (StataCorp, College Station, TX, USA).

3. Results

Compared with control subjects, cases were more likely to live on Kyushu Island but outside Fukuoka Prefecture and were less likely to live in Okinawa Prefecture and to have older siblings (Table 1). There were no differences between cases and control subjects with regard to age, smoking, or education.

There was no significant deviation from the Hardy–Weinberg equilibrium in the cases or in the control subjects ($P = 0.073$ and 0.206, respectively).

Compared with a reference group of women with the TT genotype of *IL*3 SNP rs40401, those with the CC genotype had a significantly increased risk of rhinoconjunctivitis, while no significant association was observed between the TC genotype and rhinoconjunctivitis (Table 2). The positive association was slightly strengthened after adjustment for the confounders under study: the adjusted OR for the CC genotype was 1.52 (95% CI: 1.05-2.19; $P = 0.025$). This positive relationship was significant under the additive model: the adjusted OR was 1.23 (95% CI: 1.02-1.47; $P = 0.027$). Under the dominant or recessive model, on the other hand, the positive association fell just short of the significance level ($P = 0.096$ and 0.051, respectively). The statistical power calculation revealed that, using our sample size, we could detect the gene-disease association for an OR of 1.562 with an accuracy of more than 80% at a significance level of 0.05 with a two-sided alternative hypothesis under the recessive model.

There was no significant multiplicative or additive interaction between *IL*3 SNP rs40401 and smoking with respect to rhinoconjunctivitis (Table 3).

Women with one or more older siblings had a significantly lower prevalence of rhinoconjunctivitis than those without older siblings did in this population [12]. Compared with subjects with the TT or TC genotype of *IL*3 SNP rs40401 who had one or more older siblings, those with the CC genotype who had no older siblings had a 2.33-fold increased risk of rhinoconjunctivitis; nevertheless, neither the multiplicative nor the additive interaction was significant (Table 4).

4. Discussion

To our knowledge, this is the first study to show a significant positive association between *IL*3 SNP rs40401 variant and the risk of rhinoconjunctivitis. A study of Koreans aged 7–80 years including 477 cases and 158 control subjects demonstrated that, compared with the TT genotype of *IL*3 SNP rs40401, the CC genotype was significantly associated with a reduced risk of asthma [3]. In a study in China, the CC genotype of SNP rs40401 was significantly inversely related to the risk of asthma under the recessive model in a initial sample consisting of 170 cases and 347 control subjects, but this inverse relationship was not validated in another