配列の差に基づき分離する PCR/DGGE 法を用いて行った。第１期参加者に関しては生後２年後、第２期参加者は生後１年後にアレルギー発症の状況に関してのアンケート調査を行った。

（倫理面への配慮）

上記研究における幼児ボランティアは、妊娠８ヶ月～９ヶ月目の母親学級にて病院長を通じて協力要請の説明文章を出し、参加承諾の同意を得たもののみを対象として行った。得られたサンプルはすべて匿名で扱い、得られたデータは外部には漏れぬよう厳重に保管している。以上の研究計画は京都大学倫理委員会の承認を得ている。

C．研究結果

第一期参加者の２年後の追跡調査の結果、36名の登録者中28名より回答が得られた。第二期参加者の１年後の追跡調査では 50 名の登録者中43名より回答が得られた。全回答者71名中3名がアトピー性皮膚炎、2名が喘息、5名が食物アレルギーの自覚症状を報告している。食物アレルギー発症の５名中４名は臍帯血中の IgE が0.5 unit以上と比較的高い値であったのに対し、アトピー性皮膚炎および喘息罹患者の５名全員の臍帯血 IgE 値は0.5 unit 以下と比較的低い値であった。生後３日間に抗生物質の連続投与を受けた被験者５名のうち２名が食物アレルギーを発症しており、抗生物質投与による腸内細菌叢形成の撹乱と食物アレルギー発症に何らかの関連性があることが示唆される。実際に、抗生物質の連続投与を受けた新生児の腸管では、生後１週間に腸球菌の異常増殖が起きていることが糞便菌叢解析により明らかになっている。これらの腸内細菌叢の異常と食物アレルギー発症にどのような関連性があるかを今後解析する必要がある。

アレルギー罹患者と健常者の糞便中の総細菌数には有意な差は見られなかった。菌叢に関しては、アレルギー症状を示す10名中９名から免疫系の構築に重要といわれているビフィズス菌の定着が生後２ヶ月以内に観察された。残りの１名にはビフィズス菌の定着が観察されなかった。この被験者は生後０日目から３日目までの間に連続的な抗生物質の投与が行なわれておりその影響が疑われる。食物アレルギー以外のアレルギー発症者に見られる菌叢パターンの特徴としては、*Klebsiella* 属細菌が健常者に比べると少ない傾向にあった。

D．考察・結論

食物アレルギー罹患者の臍帯血 IgE 値は全体的に高い傾向を示したのに対し、その他のアレルギー罹患者にはそのような傾向は見られなかった。また５名の食物アレルギー罹患者のうち２名が抗生物質被投与者であるのに対し、その他のアレルギー罹患者には抗生物質被投与者は含まれていなかった。これらの傾向の差は、食物アレルギーとその他のアレルギーの発症機序の差異を示唆していると考えられる。

ビフィズス菌は、動物試験などにおいて、アレルギー発症に関しては抑制効果があることが示されている。しかし、今回の調査においては、ほとんどのアレルギー罹患者においてビフィズス菌の定着が生後２ヶ月以内に見られ、ビフィズス菌の腸管定着がアレルギー回避の十分条件ではないことを示している。

これまでの予備的研究により、アレルギー罹患と腸内細菌叢の関連性は、食物アレルギー罹患者と喘息・アトピー性皮膚炎罹患者とでは異なることが予想され、アレルギー型を種別して解析を行なっていく必要があると思われる。そのためには、より大規模な疫学調査が必要であり、またより迅速・簡便に精度の高い菌叢データを得る技術が必要である。今後は、リアルタイム PCR 法による高精度定量的菌叢解析および DNA マイクロアレイによる網羅的菌叢解析法を本研究プロジェクトに導入し、糞便細菌叢とアレルギー発症の関連性を詳細に総計解析し、アレルギー発症の糞便細菌マーカーを見出していくことを計画している。

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(分担課題名) 乳幼児アトピー性皮膚炎における腸内細菌叢とプレバイオティックスに関する研究

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研究要旨：食物アレルギーを有する乳幼児アトピー性皮膚炎における便中腸内細菌叢と臨床背景との関連では重症例、下痢、抗生剤投与でビフィズス菌減少している例が多かった。ビフィズス菌の低値例にオリゴ糖（ケストース）を3ヵ月内服させ、便の腸内細菌叢と皮疹重症度の推移を検討しビフズス菌の増加と皮疹重症度の改善がみられた。食物特異ＩｇＥ抗体には変化は見られなかった。

A 研究目的：乳幼児のアトピー性皮膚炎では、食物アレルギーを合併する例が多く、重症例ほど IgE 高値、多種食物アレルギーを呈している。アトピー乳児の腸内細菌叢の異常も報告されており、アトピー性皮膚炎重症度と腸内細菌叢の関連、ビフィズス菌増殖作用が期待されるオリゴ糖投与における腸内細菌叢の動きとアトピー性皮膚炎の改善効果について検討した。

B 方法：対象は当院外来を受診した５ヵ月から３歳の食物アレルギーを合併した乳幼児アトピー性皮膚炎 34 例。腸内細菌とくにビフィズス菌の低値または黄色ブドウ球菌の検出された乳幼児 13 例については、２週間の観察期間の後、ケストース（ホクレンケストース®）を１２週間、連日、水またはジュース類にまぜて服用指導した。服用開始時、服用開始６週間後、服用終了時（12 週間後）、服用終了4～8週間後の診察(皮疹重症度評価)を行い、便細菌は東海大学に郵送し検査した。服用前後の血液アレルギー検査を行った。本研究は当院倫理委員会の審査、家族の同意書を得ておこなった。

C 結果：1) アトピー性皮膚炎児の腸内細菌ビフィズス菌割合は、極端に低値を示すものから十分な割合を示すものまでみられた。ステロイド外用、特異ＩｇＥ抗体、食物アレルゲン数とビフィズス菌割合との関連はみられなかったが、下痢、抗生剤内服後および皮疹の重症度が高い例にビフズス菌が少ない傾向がみられた。

2) ケストース内服１３例の皮疹の臨床改善効果は１例を除いて改善～著明改善がみられ、服用後の皮疹重症度点数は統計学的にも有意に低下していた（図 2）。ビフィズス菌の増加は 9 例/13 例でみられ、ケストース内服後のビフィズス菌増加効果は、ビフィズス菌実数および,全菌数に対する割合のいずれに関しても服用終了前と12W後で有意差に増加していた（図 3）。皮疹改善度とビフィズス菌増加程度との間には有意の相関関係はみられなかった。大腸菌および Staphylococcus などの変化と皮疹改善度にも有意な相関関係はみられなかった。末梢血好酸球は、4 例で増加していたが、8 例で正常化または不変であった。IgE 値は低下 3 例、不変 4 例、増加は 5 例であった（表 1）。食物アレルゲンは多種アレルギーを示し、卵１２例、牛乳９例、小麦７例、大豆７例、魚介類５例であったが、アレルゲン抗体 CAP-RAST には変化はみられなかった。

D　考案：乳幼児アトピー性皮膚炎における腸内細菌叢の異常と皮膚炎の関連については、直接の因果関係は明らかにされていない。最近、乳酸菌投与によるアトピー性皮膚炎児への乳酸菌投与による皮疹改善効果は食物アレルギー合併例で優位に効果的であることが報告されており、食物アレルギー児への乳酸菌投与によりＩＦＮγ産生が増加、腸内アレルギー炎症を鎮める作用があることが報告されている。このようなプロバイオティクスの効果に関する検討は多いが、プレバイオティックスによる検討はなされていない。オリゴ糖（ケストース）内服により、ビフィズス菌の有意な増加、春の皮疹増悪期に皮疹の改善傾向がみられ、元来下痢しやすい例を含め便通の改善した例が多かったことは、腸内細菌叢の是正が臨床的に乳幼児アトピー性皮膚炎に有用であることを示唆していると思われる。治療効果の判断には二重盲検法で症例を増やして検討する必要があると思われた。

E 結語：食物アレルギーを有する乳幼児アトピー性皮膚炎では腸内細菌叢のビフィズス菌が低値を示す例があり、オリゴ糖（ケストース）内服による腸内細菌叢の是正と皮疹の改善効果がみられた。食物アレルギーによる腸のアレルギー炎症と細菌叢への影響が皮膚炎の悪化に関連している可能性が示唆された。

F　健康危険情報　介入群になし

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H．知的財産権の出願・登録状況

取得なし

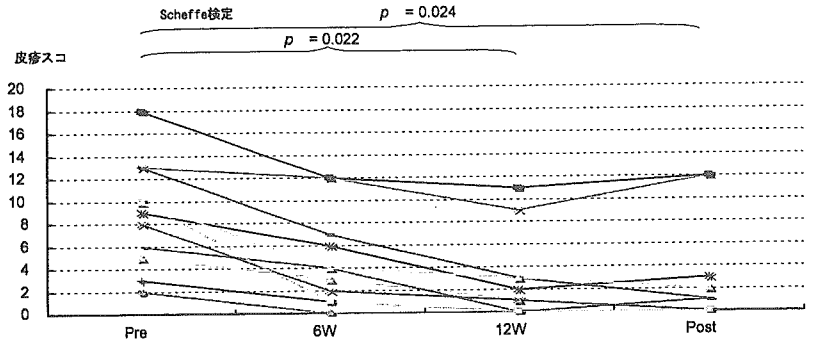

図１　ケストース内服前後の皮疹スコアの推移

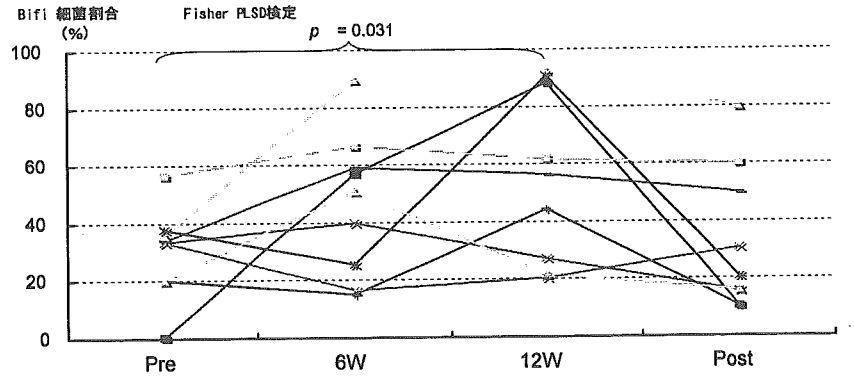

図２　ケストース内服前後のビフィズス菌割合%の推移

表１　食物アレルギーを合併したアトピー性皮膚炎乳幼児のオリゴ糖内服後の変化

	性	年齢	重症度	ビフィズス菌の変化	皮疹評価	好酸球	前 IgE 値	IgE変化
1	F	5m	重症	著明増加	著明改善	正常化	139	不変
2	M	5m	重症	著明増加	改善	改善	67	低下
3	M	6m	中等症	増加	改善	正常化	69	軽度増加
4	F	11m	中等症	変化ナシ	改善	正常不変	387	軽度低下
5	M	1y2m	中等症	増加	著明改善	正常不変	999	軽度増加
6	M	1y4m	中等症	一時増加	改善	増加	309	増加
7	M	2y1m	重症	低下	重症不変	増加	248	不変
8	F	2y3m	重症	増加	改善	正常不変	1972	高値不変
9	F	2y4m	中等症	増加	改善	nd	336	nd
10	F	2y6m	中等症	著明増加	改善	正常不変	659	増加
11	M	2y7m	中等症	著明増加	改善	軽度増加	3588	低下
12	M	3y1m	軽症	増加後低下	下痢改善	低下	1574	増加
13	M	3y4m	軽症	増加	改善	増加	6430	高値不変

地域集団でのコホート研究による便中細菌診断妥当性の研究

沖縄県石垣市乳幼児におけるアトピー性皮膚炎（Atopic dermatitis: AD）追跡調査に関する研究-乳幼児アトピー性皮膚炎における血清 Thymus and activation-regulated chemokine（TARC）の臨床的意義-

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研究要旨

私どもは、2001 年より、沖縄県石垣市において、乳幼児における AD の有病率および発症率について前向き追跡調査を行っている。対象は沖縄県石垣市小児(1-6 才)で、2001 年 631 例、2002 年 836 例、2003 年 844 例、2004 年 764 例、2005 年 799 例で、合計 3854 例を皮膚科専門医による視診により AD 診断を行い、大規模調査により、血清 Thymus and activation-regulated chemokine（TARC）の臨床的意義の高いことを確認した。

A. 研究目的

アトピー性皮膚炎(Atopic dermatitis. AD)は、ヘルパーT 細胞(Th1/Th2)のパラダイムおいて Th2 細胞が優位であり、局所的また全身的に Th2 細胞ケモカインの TARC (Thymus and activation-regulated chemokine, CCL17)の発現が増加している。血中 TARC は、AD の重症時に著増することがよく知られているが、乳幼児におけるそのデータは少ない。今回、その臨床意義について一般健常児および AD 児において、血清 TARC 値を継続的に測定し、血清 IgE 値の推移と比較検討した。

B. 研究方法

対象は、沖縄県石垣市保育園児 998 例(男児 526 例、女児 472 例、0-5 才)で、このうち 340 例については継続調査が可能であった。血清 TARC 値を ELISA 法(SD-8864, 塩野義製薬)で測定し、血清総 IgE 値を IRMA 法で測定した。全対象例に対し、U.K. Working Party diagnostic criteria for AD 質問表の問診を行い、皮膚科専門医が AD の診断を行った。なお、同時に血清 IgE 値(IRMA 法) を測定し、230 IU/mL 以上を異常高値とした。本研究は、九州大学病院倫理委員会における審査を受け、承認されている。本研究に参加した対象児は全例、その保護者により、研究目的・方法について、文書による説明を受け、同意を得ている。

C. 研究結果

健常児群の平均 TARC 値(pg/ml)は、0 才 630.8、1 才 524.9、2 才 494.3、3 才 479.0、4 才 465.3、5 才 426.0 と、年齢とともに低下したが、AD 児群では各々515.5、604.6、539.2、604.3、467.8、412.8 と年齢との関連はなかった。両群とも男・女児の間で差はなかった。一方、健常児・AD 児両群とも IgE 値(IU/mL)は年齢とともに上昇した(健常児 0 才 34.6、1 才 76.5、2 才 79.8、3 才 136.9、4 才 180.2、5 才 241.8: AD 児

各々、70.5、109.6、377.4、1081.0、288.9、625.1)。両群とも、TARC 値と IgE 値に相関を認めなかったが、AD 例の TARC および IgE 値とも健常例に比べ有意に高値であった。継続追跡可能であった 340 例での TARC 値の推移は、AD 持続 6 例で 858.3→830.2、AD 治癒 30 例で 569.9→526.2、AD 発症 17 例で 439.3→432.1、健常 287 例で 493.2→443.5 で、AD 治癒と健常例は有意な減少を認めた。これらの例の IgE 値の推移は、1464.0→2550.2、502.9→499.9、369.4→356.3、108.9→197.8 で、AD 持続と健常例は有意な上昇を認めた。

D. 考案

気管支喘息患者などのアレルギー性疾患で血清 TARC 値の病勢検討が行われているが、本研究のように、アトピー性皮膚炎を対象とした、かつ、乳児および小児での、健常例と比較した、大規模な疫学調査の報告はいまだない。したがって、そのデータは日本人のエビデンスとして、非常に価値が高いと思われる。また、今後血清 TARC 値の臨床面での利用価値が高くなるとも考えられる。

E. 結論

血清 TARC 値は、IgE に比べて AD の病勢をよく反映することが示唆された。

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研究成果の刊行に関する一覧表（平成１７年度）

出順：白川太郎、清野宏、出原賢治、古賀泰裕、園元謙二、中山二郎、柴田瑠美子、林純、

発表者氏名	論文タイトル	発表誌名	巻号	ページ	出版年
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Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2006;139:25–30
DOI: 10.1159/000089519

Received: May 23, 2005
Accepted after revision: August 18, 2005
Published online: November 3, 2005

Lack of Association between the *IL13* Variant Arg110Gln and Susceptibility to Cedar Pollinosis in a Japanese Population

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Key Words
Allergic rhinitis · Candidate gene · Hay fever · Interleukin-13 · Japanese cedar pollinosis · Single nucleotide polymorphism

Abstract
Background: Interleukin (IL)-13 has come to be appreciated as a molecule critically involved in allergic inflammatory responses. Recent studies revealed that a common variant in the coding region of the *IL13* gene, Arg110Gln, has been implicated in the development of asthma and atopy. ***Methods:*** To assess whether the *IL13* variant Arg110Gln is associated with cedar pollinosis, one of the most common atopic diseases in the Japanese population, we examined the Arg110Gln variant using PCR-RFLP to compare the genotype and allele frequencies between 95 patients with cedar pollinosis and 95 healthy control subjects. Relationships between the Arg110Gln variant and the pollinosis-related traits, e.g. rhinitis severity, eosinophil counts in nasal secretion and serum total and allergen-specific IgE levels, were also investigated. ***Results:*** The frequencies of the minor allele Gln110 were 25.8% in patients with cedar pollinosis and 30.9% in healthy control subjects ($p > 0.05$). There was also no significant difference in the genotype frequencies between cases and controls ($p > 0.05$). In addition, we found no significant association of the Arg110Gln variant with any of the pollinosis-related phenotypes ($p > 0.05$). ***Conclusions:*** Our data suggest lack of evidence for identifying the variant Arg110Gln at the *IL13* locus as a genetic risk factor involved in the development of Japanese cedar pollinosis.

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1018–2438/06/1391–0025$23.50/0

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Introduction

The origin of allergy may be strongly influenced by a variety of environmental exposures; however, host susceptibility and a variety of genes are also likely to be involved in the etiology and pathogenesis of allergic diseases such as asthma and hay fever [1–3]. Japanese cedar pollinosis (JCP) is a springtime hay fever caused by inhalation of the pollen of Japanese cedar *(Cryptomeria japonica)*, representing a major health problem in Japan because of its high prevalence, severe symptoms, impairment of the patient's quality of life and expenses in controlling the disease [4–6]. Recently, several candidate genes such as the *FCER1B* gene [7], the *IL4RA* gene [8], the *EPO* gene [8, 9] and the *ADAM33* gene [10], have been reported to underlie JCP and its intermediate phenotypes, suggesting a contributory role of genetic factors in the development of this common atopic disorder.

The type 2 cytokine IL-13, which shares signaling pathways and many biological activities with IL-4, plays a pivotal role in the generation of allergic airway inflammation [11–13]. To date, numerous genetic analyses have indicated that the gene encoding human IL-13 (located on chromosome 5q31) is implicated in the development of asthma and atopy [14, 15]. Of the *IL13* gene, Arg110Gln, which is a functional single nucleotide polymorphism (SNP) in the coding region [16, 17], has been comprehensively studied and has been found to be associated with asthma phenotypes in ethnically diverse populations [18–23]. Furthermore, recent genetic association studies in the German population [24] and Chinese samples [25] suggested a potential role of the *IL13* variant Arg110Gln (referred to as Arg130Gln in their reports) for heightened IgE production and atopic sensitization in allergic rhinitis/hay fever. To address whether this coding SNP affects susceptibility to JCP, the most common hay fever in Japan, we performed a case-control study in a Japanese population.

Subjects and Methods

Subjects and Phenotypes

The present study was performed with the approval of the Ethical Committee of the RIKEN Yokohama Institute, and written informed consent was obtained from all participants. 95 unrelated adult individuals with JCP and 95 age-matched unrelated healthy controls were enrolled in the study. All subjects were from the population of the Kinki area (west Japan).

The phenotypic characteristics of recruited subjects have been described in detail elsewhere [10] and are summarized in table 1. Briefly, of 95 patients with JCP, 5 cases (5.3%) were mild, 22 cases (23.2%) were moderate and 68 cases (71.6%) were diagnosed as severe according to the scores of three main nasal symptoms (sneezing, rhinorrhea and nasal obstruction) based on the clinical severity classification for allergic rhinitis (Okuda's method), as previously described [26]. None of the patients had a history of asthma and allergen-specific immunotherapy. The control subjects were all symptom free, had no history of atopic disorders and had negative allergen-specific IgE (<0.7 arbitrary unit/ml) in serum against house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), Japanese cedar pollen and three other common pollens in the study area (orchard grass, ragweed and *Artemisia*). The geometric mean of serum total IgE levels was 162.5 (range 5.3–10,000) IU/ml in cases and 30.0 (range 3.2–240) IU/ml in healthy controls. Patients with JCP had higher total IgE levels than control subjects (mean ± SD: 2.21 ± 0.51 vs. 1.48 ± 0.51 log IU/ml; $p < 0.0001$, t test).

Table 1. Phenotypic characteristics of recruited subjects

Category	Cases n = 95	Controls n = 95
Total serum IgE levels (means ± SD)		
log IU/ml	2.21 ± 0.51	1.48 ± 0.51
RAST positive to Japanese cedar pollen	95 (100%)	0 (0.0%)
RAST positive to house dust mites	43 (45.3%)	0 (0.0%)
Eosinophil positive in nasal secretions	82 (86.3%)	NA
Rhinitis severity		
Mild	5 (5.3%)	NA
Moderate	22 (23.2%)	NA
Severe	68 (71.6%)	NA

Genotyping

DNA samples were extracted from whole peripheral blood of study subjects by standard methods. PCR reaction was performed with 5 ng of template genomic DNA, in a 10-μl solution consisting of 13.75 pmol of each primer of 5′-tgacctctttgtcctgcag-3′ for forward and 5′-tgatgctttcgaagtttcag*tagatc*-3′ for reverse (italic nucleotides modified to create a *Bgl*II restriction site), 1.1 μl of 10× Vogelstein buffer (pH 8.8), 0.55 μl of 78 m*M* $MgCl_2$, 0.55 μl of 25 m*M* each dNTPs and 0.55 U of Ex-*Taq* DNA polymerase (TaKaRa Bio, Otsu, Japan). Thermocycling started with an initial denaturation step for 2 min at 95°C, and then 37 cycles of denaturation for 30 s at 94°C, annealing for 30 s at 55°C and extension for 30 s at 72°C, with a final extension step for 7 min at 72°C. A 263-bp PCR fragment including the Arg110Gln polymorphism was then digested by addition of 3 U *Bgl*II (TaKaRa Bio) overnight at 37°C. The digestion products were visualized on a 4% agarose gel stained with ethidium bromide.

Statistics

Statistical analysis was performed using SPSS 10.0J for Windows (SPSS, Chicago, Ill., USA). The Hardy-Weinberg equilibrium was assessed by χ^2 test. The genotype and allele frequencies for the *IL13* variant Arg110Gln in cases and control subjects were compared using Pearson's χ^2 test. If an expected number was less than 5, Fisher's exact test was used. Quantitative traits relating to rhini-

Table 2. Genotype and allele frequencies for Arg110Gln variant

Category	Cases n = 95	Controls n = 94	Odds ratio (95% CI)	p value
Genotype				
Arg/Arg	0.568	0.479	–	
Arg/Gln	0.347	0.426	0.69 (0.38–1.26)	0.226
Gln/Gln	0.084	0.096	0.74 (0.26–2.08)	0.568
Allele				
Arg	0.742	0.691	–	
Gln	0.258	0.309	0.78 (0.50–1.22)	0.275
Major homozygote	0.568	0.479	–	
Minor homozygote + heterozygote	0.432	0.521	0.70 (0.39–1.24)	0.217
Major homozygote + heterozygote	0.916	0.904	–	
Minor homozygote	0.084	0.096	0.87 (0.32–2.36)	0.782

In healthy controls, 94 samples were successfully genotyped. The reference category was assigned an odds ratio of 1.00. CI = Confidence interval.

Table 3. Arg110Gln genotypes and total serum IgE levels

Category	Cases n = 95	Controls n = 94	Total n = 189
Total IgE (means ± SD), log IU/ml			
Arg/Arg	2.196 ± 0.442	1.486 ± 0.490	1.873 ± 0.583
Arg/Gln	2.263 ± 0.585	1.539 ± 0.544	1.866 ± 0.666
Gln/Gln	2.097 ± 0.632	1.213 ± 0.459	1.629 ± 0.697
p value	0.676	0.231	0.188[a]

In healthy controls, 94 samples were successfully genotyped.
[a] Analysis using a general liner model incorporating disease status (case or control) as a covariate.

tis severity and nasal eosinophila in patients with JCP were also analyzed with χ^2 test. Association of the Arg110Gln genotypes with total serum IgE levels (logarithm transformed) and cedar pollen-RAST scores was examined by ANOVA and general liner model. Nonparametric tests were employed to analyze associations between Arg110Gln genotypes and cedar pollen-specific IgE values in patient sera. Two-tailed p values of less than 0.05 were considered statistically significant.

Results

In our study population, the distributions of Arg110-Gln genotypes of the *IL13* gene were in Hardy-Weinberg equilibrium, and the overall allele frequencies for Arg110 and Gln110 were 0.717 (271/378) and 0.283 (107/378), respectively. No significant association was detected between the Arg110Gln variant and susceptibility to JCP ($p > 0.05$, table 2). Moreover, this variant was not significantly associated with rhinitis severity and nasal eosinophila in patients with JCP (outlined in table 1). The frequency of the minor allele Gln110 was 0.278 in severe cases compared to 0.250 in mild-to-moderate cases (odds ratio = 1.15, 95% confidence interval = 0.57–2.35; $p > 0.05$), and was 0.308 in patients with eosinophil-positive compared to 0.250 in those with eosinophil-negative nasal secretion (odds ratio = 1.33, 95% confidence interval = 0.54–3.30; $p > 0.05$).

An analysis was also carried out on the relationship between investigated genotypes and IgE measurements. We did not find significant differences in total serum IgE levels among the Arg110Gln genotypes in JCP patients, healthy controls and both groups combined ($p > 0.05$, table 3). There was no correlation between the Arg110Gln genotype and cedar pollen-RAST scores in our study population ($p > 0.05$). The Arg110Gln variant was also not significantly associated with cedar pollen-specific IgE val-

ues in sera from patients ($p > 0.05$). A tendency to lower cedar pollen-RAST scores was observed in those homozygous for Gln110 compared to those homozygous for Arg110 and heterozygous combined, but statistical significance was not reached ($p = 0.067$). In addition, we analyzed the allele and genotype frequencies of the Arg110Gln variant in JCP-affected individuals with or without sensitization to house dust mites and did not observe any significant association ($p > 0.05$).

Discussion

The *IL13* gene encodes a T-lymphocyte-derived cytokine, IL-13, which is produced primarily by activated Th2 cells. IL-13 has been shown to be an important and unique mediator of allergic processes such as IgE production, eosinophilic inflammation, mucus hypersecretion and airway hyperresponsiveness [27]. Recently, numerous SNPs have been identified at the *IL13* locus, and a significant association has been found between these SNPs and asthmatic and/or allergic phenotypes in several populations of distinct ethnic background [18–23, 28–32]. The role of a common coding SNP in the fourth exon that causes a substitution of the amino acid arginine by glutamine at position 110 of the mature protein (Arg110Gln) in the development of asthma and atopy has been widely investigated in ethnically diverse groups; however, less attention was directed to the genetic influence of this functional SNP on the risk of allergic rhinitis/hay fever.

This study represents an evaluation of the Arg110Gln variant in the *IL13* gene as a susceptibility locus for JCP, one of the most common seasonal allergic diseases in the Japanese population. Using a case-control study, we evaluated the Arg110Gln variant for evidence of association to JCP and related phenotypes. Based on the results, we found no evidence to support a significant association between the Arg110Gln variant and the diagnosis of JCP. We also noticed no significant association between this coding SNP and cedar-pollinosis-related traits including serum levels of total and allergen-specific IgE, eosinophil counts in nasal secretion and clinical severity of rhinitis. Our findings might indicate that genetic variation in Arg110Gln at the *IL13* locus is not likely to be involved in the development of JCP.

Of course, the lack of association in our study could reflect a type II error. However, a previous case-control study has shown no significant association of the *IL13* variant Arg110Gln with self-reported hay fever in a large cohort of Germans [24]. Moreover, there was no relationship between this coding SNP and the diagnosis of allergic rhinitis due to *Artemisia* pollen and/or Der p 1 in a Chinese population [25]. For atopy-related phenotypes, Nieters et al. [24] found a marginal significance for the association ($p = 0.046$) of the Arg110Gln variant with in vitro specific IgE responses to common inhalant allergens in their study subjects, being almost completely of Caucasian origin, while Wang et al. [25] showed a borderline effect ($p = 0.039$) of this SNP on serum total IgE levels, but not on specific IgE concentrations against either *Artemisia* pollen or Der p 1, in Chinese patients with allergic rhinitis. Most recently, Miyazawa et al. [33] also reported a negative association of this SNP with JCP susceptibility and anti-Cry j 1 antibody titers in a small Japanese study cohort. Combined with the results of our study, these facts suggest that the Arg110Gln variant in *IL13* is unlikely to represent a major determinant in the development of hay fever and allergic sensitization in ethnically diverse populations.

Hay fever is a typical atopic disease characterized by type I hypersensitivity reactions following induction of IgE-sensitized mast cell release by allergenic pollens. Although T-cell activation is also a characteristic feature of allergic disorders in the upper and lower airways, increased T-cell activation is not consistently found in hay fever [34, 35]. This may explain the lack of association between the Arg110Gln variant of the *IL13* gene (encoding cytokine IL-13 produced principally by activated Th2 cells) and susceptibility to hay fever seen in our study as well as in others [24, 25, 33].

It should also be mentioned that several previous case-control association studies did not reveal any relationship between the *IL13* variant Arg110Gln and asthma per se or asthma-related traits including bronchial hyperresponsiveness, elevated total IgE levels and positive allergen skin tests [28, 36, 37]. However, these data were in contrast to studies showing an association of this SNP with asthma susceptibility [18, 23] or allergy phenotypes [20, 21, 23]. The effects of racial and ethnic differences in environmental and/or genetic risk factors on the development of complex common diseases [38] may account for the conflicting findings. Interestingly, a significant correlation was well demonstrated between the Gln110 variant and high total IgE levels [19, 29, 30], but not specific IgE against common allergens [19, 31], in an unselected population of German children. Consequently, it might be deduced that rather than controlling allergen-specific IgE responses, the Arg110Gln variant at the *IL13* locus may play a potential role in total serum IgE production during the early life.