

## Predominant expression of 950delCAG of IL-18R $\alpha$ chain cDNA is associated with reduced IFN- $\gamma$ production and high serum IgE levels in atopic Japanese children

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**Background:** We previously reported that serum IgE levels were negatively correlated with the amount of IFN- $\gamma$  produced by phytohemagglutinin-stimulated or IL-12-stimulated PBMCs and that one of the mechanisms of the pathogenesis of atopy was the reduced IFN- $\gamma$  production, which led to upregulated IgE production.

**Objective:** IL-18 is also known to be a strong inducer of IFN- $\gamma$  production. However, it has not yet been determined whether IL-18 is associated with atopic disease.

**Methods:** We investigated the response to IL-18 or IL-12 stimulation and the sequence of IL-18 receptor (IL-18R)  $\alpha$  chain cDNA in 41 nonatopic controls and 39 atopic patients.

**Results:** Serum IgE level was negatively correlated with IFN- $\gamma$  production by PBMCs stimulated with IL-18. The IL-18R  $\alpha$  chain cDNA of atopic patients was sequenced. We identified a 3-base deletion of the IL-18R  $\alpha$  chain cDNA (950delCAG), which was generated by alternative splicing, as determined on the basis of genomic sequence data for the IL-18R  $\alpha$  chain gene. PBMCs with the predominant expression of 950delCAG significantly showed the reduced IFN- $\gamma$  production after IL-18 stimulation. There was a significant difference in the expression pattern of the IL-18R  $\alpha$  chain transcript between the atopic patients and the nonatopic controls.

**Conclusion:** According to these results, the dominant expression of the 950delCAG transcript of IL-18R  $\alpha$  chain cDNA, which was associated with reduced IFN- $\gamma$  production by IL-18 stimulation and high serum IgE levels, is predisposition to some atopic diseases. (J Allergy Clin Immunol 2002;109:669-75.)

**Key words:** Atopy, IL-18, IFN- $\gamma$ , IgE, IL-18 receptor

### Abbreviations used

950delCAG: Three-base deletion of the IL-18 receptor  $\alpha$  chain cDNA

NK: Natural killer

PHA: Phytohemagglutinin

IL-18R: IL-18 receptor

A variety of biological functions have been associated with human IL-18, including induction of proliferation of activated T cells, enhancement of natural killer (NK) cytotoxicity, induction of IFN- $\gamma$  and GM-CSF production, and promotion of a T<sub>H</sub>1-type T-cell response.<sup>1-4</sup> The activity of IL-18 is via an IL-18 receptor (IL-18R) complex. This IL-18R complex is composed of a binding chain termed IL-18R  $\alpha$ , a member of the IL-1R family previously identified as the IL-1R-related proteins, and a signaling chain, also a member of the IL-1R family. The IL-18R complex recruits the IL-1R-activating kinase and TNF-associated factor 6, which phosphorylates nuclear factor  $\kappa$ B-inducing kinase, with subsequent activation of nuclear factor  $\kappa$ B.<sup>5-7</sup>

With respect to IL-18 and atopic diseases, the data of Kodama et al<sup>8</sup> support a role for IL-18 in the complex pathogenesis of allergic inflammation in which IL-18 limits the development of the local inflammatory response to antigen. In vivo, the synergistic action of IL-12 and IL-18 is necessary to prevent T<sub>H</sub>2-like cell differentiation, and this consequently inhibits the development of airway symptoms in a mouse model of allergic asthma.<sup>9</sup> A contrary result has also been reported. IL-18 has the potential to stimulate basophils, but when coadministered with IL-12, it exhibits an antiallergic action in vivo.<sup>10</sup> IL-18 promotes expression of the T<sub>H</sub>2 phenotype in vivo, potently induces allergic sensitization,<sup>11</sup> induces T<sub>H</sub>2 cytokine and CD154 expression, and can contribute to CD4<sup>+</sup> T-cell-dependent, IL-4-independent IgE production.<sup>12</sup>

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**Abbreviations used**

HDM: House dust mite  
TCR: T-cell receptor

We previously reported that serum IgE level was negatively correlated with the amount of IFN- $\gamma$  secreted by PBMCs and that IFN- $\gamma$  production by IL-12-stimulated PBMCs in an atopic group was lower than that in a control group.<sup>13,14</sup> Furthermore, serum IgE level was negatively correlated with IFN- $\gamma$  production by PBMCs stimulated with IL-12, one of the reasons being that reduced IFN- $\gamma$  production after IL-12 stimulation was associated with heterozygous IL-12R  $\beta$ 2 mutations in atopic subjects.<sup>15</sup>

IL-18, a novel inflammatory cytokine that shares biological functions with IL-12, is known as a strong IFN- $\gamma$ -inducing factor. In this study, we examined IFN- $\gamma$  production in PBMCs after stimulation with IL-18 and the IL-18R  $\alpha$  chain cDNA sequence. We show that predominant expression of 950delCAG of IL-18R  $\alpha$  chain cDNA is associated with reduced IFN- $\gamma$  production after stimulation with IL-18 and high serum IgE levels in some atopic patients.

## MATERIALS AND METHODS

### Patients and control subjects

All of the atopic and control patients were outpatients at our hospitals. All were free of acute infection at the time of testing. The atopic group consisted of 39 children who had IgE levels higher than 150 IU/mL, specific IgE levels higher than 3.5 IU/mL, and clinical symptoms such as bronchial asthma or atopic dermatitis. The mean age  $\pm$  1 SD of the atopic patients was 6.9  $\pm$  4.4 years, and their mean IgE  $\pm$  1 SD level was 2062.4  $\pm$  3240.2 IU/mL. The diagnosis of bronchial asthma was made according to the criteria of the American Thoracic Society, and that of atopic dermatitis was made according to the criteria of Hanifin. Specific IgE antibodies for house dust, *Dermatophagoides*, hen egg, and cow milk were measured with a fluoroenzyme immunoassay by means of a Uni-Cap assay kit (Pharmacia, Uppsala, Sweden). A specific IgE level higher than 3.5 IU/mL was considered positive. No patients had been receiving systemic steroids.

Each of the 41 nonatopic controls had a negative history of atopic disease. Their serum IgE levels were lower than 150 IU/mL, and the specific IgE levels for the 4 allergens were lower than 3.5 IU/mL. The mean age  $\pm$  1 SD of the nonatopic controls was 4.8  $\pm$  6.7 years, and their mean IgE  $\pm$  1 SD level was 42.2  $\pm$  35.1 IU/mL.

Informed consent was obtained from all subjects or their parents.

### Cell preparation

PBMCs were isolated from 5 mL heparinized blood of control donors and patients by gradient centrifugation in Ficoll-Paque (Pharmacia). PBMCs were suspended at a density of 10<sup>6</sup>/mL in RPMI 1640 medium supplemented with 10% heat-inactivated FCS, L-glutamine (2 mmol/L), penicillin (100 U/mL), and streptomycin (100  $\mu$ g/mL).

### Cell culture

PBMCs (10<sup>6</sup>/mL) were cultured in the presence or absence of 10  $\mu$ g/mL phytohemagglutinin (PHA; Gibco BRL, Grand Island, NY), 5 IU/mL recombinant human IL-12 (R & D systems, Inc, Wiesbaden,

Germany), or 400 ng/mL recombinant human IL-18 for 24 hours in a final volume of 1 mL in a round-bottom tube (Falcon 2059, Becton Dickinson Labware, Lincoln Park, NJ) at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>.<sup>14</sup> The recombinant human IL-18 used had been prepared in our laboratory through use of an *Escherichia coli* expression system (according to an unpublished method developed by Kato et al). The endotoxin level of the recombinant human IL-18 was less than 0.1 pg per 1  $\mu$ g of the protein.

### Assays of cytokines

Culture supernatants in the test tubes incubated for 24 hours were spun to remove cells after the cultures. IFN- $\gamma$  concentrations were measured through use of a human IFN- $\gamma$  ELISA kit (Ohtsuka, Tokyo, Japan); the detection limit was 15.6 pg/mL.<sup>14</sup> Results of some samples were confirmed by duplicate measurement ( $P < .0001$ ;  $r = 0.994$ ).

### IgE assay

Plasma samples obtained from heparinized blood were stored at -30°C. Plasma IgE concentrations were determined with a chemiluminescent enzyme immunoassay. The values were regarded as the serum IgE concentrations.

### Sequencing of IL-18R $\alpha$ chain cDNA

RNA was extracted from PBMCs cultured in the presence of PHA for 24 hours through use of an Isogen kit (Nippon Gene, Tokyo, Japan). Fragments of IL-18R  $\alpha$  chain cDNA were amplified, ligated to a T-vector (Novagen, Madison, Wis), and sequenced through use of an ABI 377 DNA sequencer (Applied Biosystems, Indianapolis, Ind). The conditions for the PCRs were 94°C for 1 minute, 55°C for 1 minute, and 72°C for 2 minutes.

For concise detection of 950delCAG, 40 cycles of PCR were performed through use of the sense primer 5'-<sup>891</sup>ATTGCACTGTG-GCCAGCACG-3' and the antisense primer 5'-<sup>991</sup>TCCTCTGTG-GAAGACGTGGC-3'. The nucleotide was numbered according to the Gene Bank Database U43672. The fragments were electrophoresed on 15% polyacrylamide gel to detect the size difference between normal and mutant fragments. The fragments were simultaneously ligated to the T-vector and sequenced through use of the autosequencer.

### Amplification of the genomic region of 950delCAG of IL-18R $\alpha$ chain

Genomic DNA was purified from a polynuclear cell fraction with a Sepa Gene (Sanko Jyunkyaku, Tokyo, Japan), used according to the manufacturer's instructions. The conditions for detection of 950delCAG from genomic DNA amplified by PCR were 94°C for 1 minute, 55°C for 1 minute, and 72°C for 2 minutes for 40 cycles. PCR was performed through use of the sense primer 5'-<sup>909</sup>CGGGAGGCACAGACACCAAA-3' and the antisense primer 5'-<sup>982</sup>GAAGACGTGGCCTGGGATAT-3'.

### Statistical analyses

The significance of the difference between the 2 groups was analyzed by means of the Student *t* test. A multiple regression model was used to simultaneously evaluate the effects of the log-transformed independent variables on IFN- $\gamma$  production and incorporate the effect of IL-12, IL-18, or PHA as a categorical grouping variable.

Association of the differences in the expression pattern of 950delCAG of IL-18R  $\alpha$  chain transcript and IgE or IFN- $\gamma$  production stimulated by IL-18 was confirmed by ANOVA and then analyzed by Fisher's protected least significant difference test.

Differences in the expression pattern of 950delCAG of IL-18R  $\alpha$  chain transcript between the atopic group and the control group were compared through the use of  $\chi^2$  statistics.

## RESULTS

### Correlation between serum IgE levels and IFN- $\gamma$ production by PHA-stimulated and IL-18-stimulated PBMCs

The IL-18-stimulated PBMCs of the atopic group ( $n = 39$ ; mean  $\pm$  1 SD =  $161.1 \pm 308.2$  pg/mL) had lower IFN- $\gamma$  production than those of the control group ( $n = 41$ ; mean  $\pm$  1 SD =  $429.0 \pm 728.7$  pg/mL;  $P = .0370$ ). We investigated the correlation between serum IgE levels and concentrations of IFN- $\gamma$  in the atopic and control subjects produced by IL-18-stimulated PBMCs. The serum IgE levels were negatively correlated with the concentrations of IFN- $\gamma$  produced by IL-18-stimulated PBMCs ( $P = .0359$ ;  $r = 0.235$ ; Fig 1). The concentrations of IFN- $\gamma$  in the atopic and control subjects produced by IL-18-stimulated PBMCs were well correlated with those produced by PHA-stimulated PBMCs ( $P = .00370$ ;  $r = 0.432$ ). The concentrations in the atopic and control subjects of IFN- $\gamma$  produced by IL-12-stimulated PBMCs were significantly correlated with those produced by IL-18-stimulated PBMCs ( $P = .00529$ ;  $r = 0.490$ ). However, in several patients, IFN- $\gamma$  was not sufficiently produced by IL-18 stimulation, though IFN- $\gamma$  was sufficiently produced by PHA or IL-12 stimulation. We used a multiple regression model to simultaneously evaluate the effects of the log-transformed independent variables on IFN- $\gamma$  production and incorporate the effect of IL-12, IL-18, or PHA as a categorical grouping variable. It showed no significant correlation between serum IgE level and IL-12-stimulated, IL-18-stimulated, or PHA-stimulated IFN- $\gamma$ .

### Three-base deletion in IL-18R $\alpha$ chain transcript

To clarify the mechanism of selectively reduced IFN- $\gamma$  production in response to stimulation with IL-18 and high serum IgE level, IL-18R  $\alpha$  chain cDNAs from atopic patients were sequenced. We identified a 3-base deletion of the IL-18R  $\alpha$  chain cDNA (*950delCAG*) in some patients. By this 3-base deletion, the codon for Ala 317 was deleted. Because the transmembrane domain of IL-18R  $\alpha$  spans Gly 330 and Tyr 351, this Ala was located in the extracellular domain. We cloned the partial genomic DNA around *950delCAG* by PCR. This deletion was not detected in the genomic DNA. The genomic sequence suggested that the *950delCAG* mutation was caused by alternative splicing (Fig 2, A).

We investigated the expression pattern of *950delCAG* of IL-18R  $\alpha$  chain transcript in PBMCs. Three patterns were identified by polyacrylamide gel electrophoresis: predominant expression of the wild-type transcript (wild/wild; Fig 2, B, lane 5), almost equal expression levels of the 2 transcripts (wild/delCAG; Fig 2, B, lane 3), and predominant expression of *950delCAG* transcript (delCAG/delCAG; Fig 2, B, lane 4). We investigated the frequency of plasmid DNA with wild or *950delCAG* from randomly selected colonies; this is derived from the PCR product of each PBMC's cDNA (Table I). Consis-

IFN-gamma (pg/ml) production  
by IL-18-stimulated PBMCs

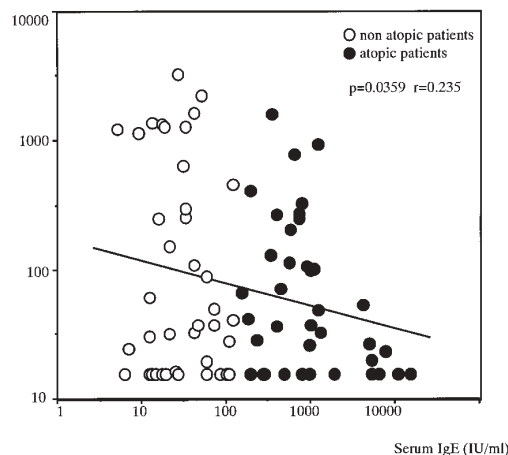


**FIG 1.** The relationship between serum IgE levels and IFN- $\gamma$  concentrations in the cultured supernatants of IL-18-stimulated PBMCs. The serum IgE levels were negatively correlated with the IFN- $\gamma$  concentrations by IL-18-stimulated PBMCs. ( $r = 0.235$ ;  $P = .0359$ ). Open circles represent nonatopic subjects; closed circles represent atopic subjects. The line is a recurrence straight line.

tent with the results of the polyacrylamide gel electrophoresis, the colonies originating from wild/wild had 6/6 to 8/8 wild-type cDNA. The colonies originating from delCAG/delCAG had 7/7 to 10/10 *950delCAG* cDNA. The colonies originating from wild/delCAG had 50~66.7% wild DNA and 50~33.3% *950delCAG* DNA.

### Expression pattern of *950delCAG* IL-18R $\alpha$ chain transcript in the atopic patients

We investigated whether the expression pattern of the *950delCAG* is associated with atopic patients. The  $\chi^2$  test revealed a significant difference ( $P = .0179$ ) in the expression pattern of *950delCAG* of IL-18R  $\alpha$  chain transcript between the atopic group and the nonatopic group (Table II). We next investigated whether there was a correlation between the expression pattern of *950delCAG* of IL-18R  $\alpha$  chain transcript and IL-18-induced IFN- $\gamma$  production. Interestingly, the expression of delCAG/delCAG significantly reduced IFN- $\gamma$  production in comparison with the expression of the wild/wild ( $P = .0080$ ; Fig 3, A). In contrast, there was no significant difference between the expression pattern of *950delCAG* of IL-18R  $\alpha$  chain transcript and IL-12-induced IFN- $\gamma$  production (Fig 3, B). People who had the expression pattern of delCAG/delCAG transcripts had high serum IgE levels in comparison with people who had the wild/wild ( $P = .0209$ ; Fig 4).

## DISCUSSION

In the present study, we showed that the concentrations of IFN- $\gamma$  produced by IL-18-stimulated PBMCs in the atopic group were significantly lower than those in

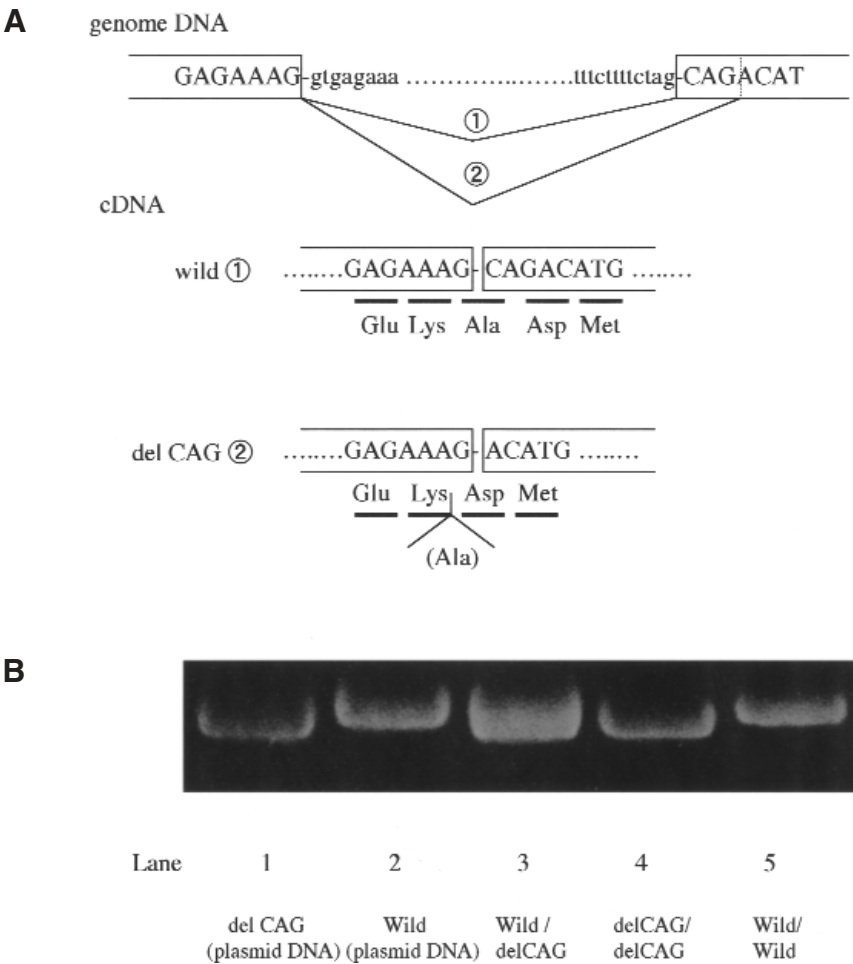


**FIG 2. A**, Wild and 950delCAG of IL-18R  $\alpha$  chain sequences of genomic DNA and cDNA. The 950delCAG was generated by alternative splicing. **B**, Three expression patterns (wild/wild, wild/delCAG, and delCAG/delCAG) identified by polyacrylamide gel electrophoresis. *Lane 1*: The template DNA is plasmid DNA with 950delCAG of IL-18R  $\alpha$  chain. *Lane 2*: The template DNA is plasmid DNA with wild IL-18R  $\alpha$  chain. *Lane 3*: The PCR product was identified as wild/delCAG. *Lane 4*: The PCR product was identified as delCAG/delCAG. *Lane 5*: The PCR product was identified as wild/wild.

**TABLE I.** Frequency of randomly selected colonies harboring wild or 950delCAG of IL-18R  $\alpha$  chain cDNA

|                            | Wild colony no./total colonies no. (%) <sup>*</sup> | 950delCAG colony no./total colonies no. (%) <sup>*</sup> |
|----------------------------|-----------------------------------------------------|----------------------------------------------------------|
| Wild/wild <sup>†</sup>     |                                                     |                                                          |
| Control 1                  | 8/8 (100%)                                          | 0/8 (0%)                                                 |
| Control 2                  | 8/8 (100%)                                          | 0/8 (0%)                                                 |
| Control 3                  | 6/6 (100%)                                          | 0/6 (0%)                                                 |
| Wild/delCAG <sup>*</sup>   |                                                     |                                                          |
| Control 4                  | 4/7 (57.1%)                                         | 3/7 (42.9%)                                              |
| Allergy 1                  | 4/6 (66.7%)                                         | 2/6 (33.3%)                                              |
| Allergy 2                  | 5/10 (50%)                                          | 5/10 (50%)                                               |
| delCAG/delCAG <sup>*</sup> |                                                     |                                                          |
| Allergy 3                  | 0/7 (0%)                                            | 7/7 (100%)                                               |
| Allergy 4                  | 0/9 (0%)                                            | 9/9 (100%)                                               |
| Allergy 5                  | 0/10 (0%)                                           | 10/10 (100%)                                             |

<sup>\*</sup>Determined by sequencing.

<sup>†</sup>Determined by polyacrylamide gel electrophoresis.

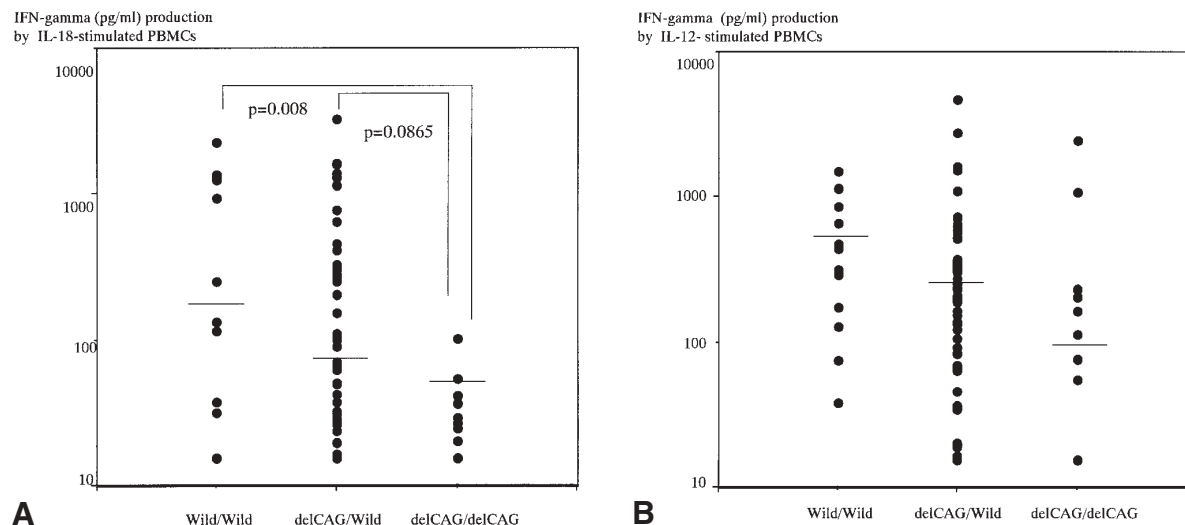


**FIG 3. A**, The relationship between expression pattern of *950delCAG* of IL-18R  $\alpha$  chain transcript and IL-18-induced IFN- $\gamma$  production. IFN- $\gamma$  production was significantly lower when delCAG/delCAG was expressed than when wild/wild was expressed ( $P = .0080$ ). Bar shows geometric mean. **B**, The relationship between the expression pattern of *950delCAG* IL-18R  $\alpha$  chain transcript and IL-12-induced IFN- $\gamma$  production. There was no correlation between the case when delCAG/delCAG was expressed and that when wild/wild was expressed or between the case when delCAG/delCAG was expressed and that when wild/delCAG was expressed. Bar shows geometric mean.

the control group. Moreover, serum IgE level was negatively correlated with the concentrations of IFN- $\gamma$  produced by PBMCs cultured with IL-18. However, in several patients, IFN- $\gamma$  production was not sufficiently induced by IL-18 stimulation, though IFN- $\gamma$  production was sufficiently induced by IL-12 or PHA stimulation. These results suggest that there might be some abnormalities in signal transduction of IL-18. Therefore, we analyzed the IL-18R  $\alpha$  chain cDNA sequence in these atopic patients. We identified a 3-base deletion of *950delCAG* of IL-18R  $\alpha$  chain cDNA in some atopic patients. The *950delCAG* mutation resulted in the deletion of 317 Ala, which was located in the extracellular domain of IL-18R  $\alpha$ . PBMCs from the patients with low IFN- $\gamma$  production stimulated by IL-18 tended to express the delCAG/delCAG transcript. Furthermore, this group showed a high serum IgE level. These results suggest that PBMCs from the patients in whom the delCAG/delCAG transcript was expressed could not suppress IgE production because of reduced IFN- $\gamma$  production by IL-18 stimulation. Reduced IFN- $\gamma$  production by IL-18-stimulated PBMCs might be caused by the impairment of the IL-18R signaling due to the deletion of Ala in the extracellular domain of IL-18R  $\alpha$  chain cDNA.

Despite the significance, the correlation between serum IgE and IFN- $\gamma$  concentrations produced by PBMCs cultured with IL-18 was weak. These results suggest that IgE is regulated by multiple factors, including cytokines and some receptors. Even cytokines IL-4 and IL-13 have been reported as IgE regulators.<sup>16</sup> The involvement of multiple factors in IgE regulation might cause the weak association between IL-18-stimulated IFN- $\gamma$  production and IgE.

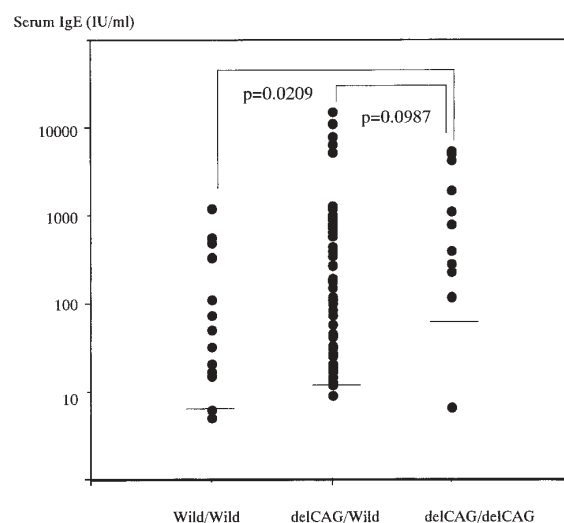


**FIG 4.** Relationship between the expression pattern of *950delCAG* of IL-18R  $\alpha$  chain transcript and serum IgE levels. The serum IgE levels in the case when delCAG/delCAG was expressed were significantly higher than those when wild/wild was expressed ( $P = .0209$ ). Bar shows geometric mean.

**TABLE II.** Relationship between the expression pattern of *950delCAG* of IL-18R  $\alpha$  chain cDNA and allergy

|         | n  | Wild/<br>wild* | delCAG/<br>wild* | delCAG/<br>delCAG* | P value     |
|---------|----|----------------|------------------|--------------------|-------------|
| Control | 41 | 9              | 30               | 2                  | $P = .0179$ |
| Atopy   | 39 | 4              | 26               | 9                  |             |
| Totals  | 80 | 13             | 56               | 11                 |             |

\*Determined by polyacrylamide gel electrophoresis.

It is assumed that *950delCAG* might cause a loss of function of the IL-18R  $\alpha$  chain. With regard to the loss of function due to *950delCAG*, there is the possibility that this mutation might result in a reduced binding affinity of the IL-18R  $\alpha$  chain to IL-18 and might result in insufficiency of signal transmission. The levels of IFN- $\gamma$  production by IL-18-stimulated PBMCs cultured for 3 days tended to be comparable to the normal level (data not shown). Therefore, PBMCs with *950delCAG* might require more time to produce IFN- $\gamma$  at the same level as those of wild IL-18R  $\alpha$  chain cDNA. This result suggests that the function of IL-18R  $\alpha$  chain cDNA with the *950delCAG* results in the insufficiency of signal transduction.

Alternative splicing transcripts of cytokines and cytokine receptor genes have been reported in allergic patients. Airway biopsy specimens from asthmatic patients were more likely to express the IL-4 alternative splice variant IL-4 $\delta$ .<sup>17</sup> An altered expression and action of the low-affinity IgE receptor Fc $\epsilon$ RII (CD23) was found in the airway smooth muscle of asthmatic patients.<sup>18</sup> Deletion of individual exons and induction of soluble murine IL-5R  $\alpha$  chain expression were also observed.<sup>19</sup> A predominant expression of alternative transcripts of cytokine and cytokine receptor genes might be one of the mechanisms of pathogenesis of atopic diseases.

It was originally considered that the major action of IL-18 was induction of IFN- $\gamma$  production by T<sub>H</sub>1 cells and NK cells, particularly in combination with IL-12.<sup>20-24</sup> In combination with IL-12, IL-18 also induces anti-CD40-activated B cells to produce IFN- $\gamma$ , which inhibits IL-4-dependent IgE and IgG1 production.<sup>25</sup> However, the functions of IL-18 in vivo are very heterogeneous and complicated. Recently, it has been reported that IL-18 enhances the IL-12-driven T<sub>H</sub>1 immune responses as well as stimulating T<sub>H</sub>2 immune responses in the absence of IL-12.<sup>26</sup> It has been reported that IL-18 enhanced eosinophil recruitment into the airways<sup>27</sup> and, in combination with IL-2, increased IL-13 secretion by NK cells and T cells.<sup>28</sup> It has also been reported that in the presence of IL-3, IL-18 induced basophils and mast cells to express high levels of IL-4, IL-13, and histamine.<sup>29</sup> Recently, IL-18 was found to increase IgE production in a CD4<sup>+</sup> T-cell-dependent, IL-4-dependent, and STAT6-dependent manner.<sup>30</sup>

We have shown that when IL-18 alone was added to PBMCs, IL-18 induced T<sub>H</sub>1-type cytokines such as IFN- $\gamma$  and that IL-18 played an important role in the inhibition of atopic diseases. This is the first report showing that some atopic diseases are caused by impairment of the IL-18 signal cascade, which downregulates IgE production. In most cases, atopic disease is caused by multiple factors. In this report, we showed that 9 of 39 atopic patients expressed *950delCAG* and reduced IFN- $\gamma$  production. We think that in these 9 patients dominant expression of *950delCAG* is one of the factors that caused elevated IgE. However, the other factors, such as IL-4 receptor and IL-13 polymorphism, might be involved in IgE elevation in these patients. The patients without dominant *950delCAG*, who showed the reduced IFN- $\gamma$  production

stimulated with IL-18, might have other polymorphisms, such as IL-18 or IL-18R  $\beta$ . We have not as yet determined what mechanism induces the predominant expression of the IL-18R  $\alpha$  chain cDNA in some atopic patients. Cytokines, viral infections, and environmental factors might be the candidate modulators of IL-18R  $\alpha$  chain transcript expression. Experiments along these lines are now under way.

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