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Review Article

Allergic disorders: A model for establishing how to prevent common disease

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Abstract

Allergy to common agents, such as plant pollens, dust mites and foods, is termed atopy. Atopy is the principal cause of the chronic inflammatory diseases of eczema (the skin), hayfever (the nose) and asthma (the lungs) in children and young adults. Atopy affects millions of individuals in Japan and other developed countries and is a major source of chronic ill health in childhood and of major health expenditure. Current treatments only control symptoms and there is an urgent need for a more fundamental understanding of the origins of atopy in order to plan more effective treatment and prevention. This may become a useful model for other common multifactorial disease.

Key words: allergy, hygiene hypothesis, IgE, interleukin-13, interleukin-4, single nucleotide polymorphisms.

Introduction

Shirakawa *et al*.[1–4] have conducted a collaborative research program examining the origins of atopy over the past 20 years and have provided evidence that human genetic variation, single nucleotide polymorphisms (SNP) and exposure to environmental factors in early childhood are the key factors in this context. Their identical twin studies[3] indicated the importance of environmental factors, as well as genetic factors, which allow us to start an intervention study for the prevention of allergic disorders.

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Single nucleotide polymorphisms within interleukin-4/interleukin-13 signaling of immunity

A revolutionary development in molecular genetic research techniques has enabled us to examine the human genome for the occurrence of genetic variants that are relevant to the immune system and to the development of allergy. We have been able to demonstrate that genetic variants, influencing a number of functions within the immune system, contribute to the atopic disorder. In particular, we have emphasized the importance of SNP within interleukin (IL)-4/IL-13 coding genes (Table 1).[1] These findings are of immediate importance for the planning of new drug therapies in atopy and asthma. However, this candidate approach, although relevant, does not allow us to identify novel genes. Therefore, we started, at SNP Research Center in Riken, a case-control study screening the whole genome for SNP that may be of interest for allergic disorders using the linkage disequilibrium analysis. After 2 years extensive work, our team has finally identified a final 37 candidate SNP for asthma (Table 2). However, allergy is a multifactorial disease and the mechanisms by which identified genetic variants interact each other have

Table 1 Odds ratios (95% confidence intervals) for interleukin (IL)-13 and its receptor genes, IL-4R and IL-13RA1, according to asthma, total serum IgE, ASE and atopy in Japanese and British populations[1]

	IL-13			IL-4Rα			IL-13Rαl	
	Gln110Arg Gln/Gln+Gln/Arg(*)	*P*	Ile50Val Ile50/Ile50(*)	*P*	Arg551Gln Arg551/Arg551+ Arg551/Gln551(*)	*P*	A1398G A1398/A1398(*)	*P*
Japanese								
Atopic asthma	1.85 (1.05–3.24)	0.033	4.42 (1.57–6.69)	< 0.0001	1.66 (0.88–3.13)	0.111	1.35 (0.76–2.41)	0.304
Non-atopic asthma	1.77 (1.01–3.10)	0.047	1.00	1.00	1.12 (0.58–2.17)	0.737	1.19 (0.67–2.10)	0.560
Asthmatics	1.81 (1.11–2.93)	0.013	1.52 (0.68–2.98)	< 0.151	1.38 (0.77–2.78)	0.264	1.27 (0.77–2.08)	0.350
Total serum IgE	1.18 (0.72–1.90)	0.508	3.09 (1.98–4.91)	< 0.0001	1.28 (0.81–2.02)	0.288	1.18 (0.72–1.93)	0.516
ASE	1.59 (1.00–2.53)	0.051	3.17 (1.98–5.07)	< 0.0001	1.26 (0.63–2.52)	0.319	1.29 (0.80–2.08)	0.296
Atopy	1.66 (1.01–2.57)	0.047	7.04 (2.08–9.88)	< 0.0001	1.59 (0.91–3.03)	0.093	1.28 (0.80–2.08)	0.305
British								
Atopic asthma	1.83 (1.13–2.99)	0.014	1.12 (0.81–2.34)	0.624	0.78 (0.45–1.24)	0.342	3.22 (1.26–8.33)	0.018
Asthma	2.14 (1.28–3.60)	0.003	1.11 (0.68–1.82)	0.770	0.73 (0.45–1.17)	0.236	2.70 (0.98–7.14)	0.053
Severe asthmatics	2.31 (1.33–4.00)	0.003	1.39 (0.74–2.13)	0.488	0.78 (0.47–1.30)	0.409	2.50 (0.87–7.35)	0.090
Total serum IgE	1.49 (0.92–2.42)	0.100	1.25 (0.30–1.47)	0.366	1.06 (0.66–1.69)	0.901	4.16 (1.61–10.86)	0.021
ASE	1.27 (0.77–2.10)	0.351	1.05 (0.29–1.28)	0.856	0.62 (0.39–1.01)	0.071	2.32 (0.85–6.45)	0.122
Atopy	1.52 (0.90–2.58)	0.118	1.23 (0.73–2.04)	0.515	0.82 (0.50–1.34)	0.520	2.63 (0.87–7.69)	0.111

ASE, allergen-specific IgE.

hardly been discussed. Using two major multivariate analysis tools, namely logistic regression (LR) and artificial neural network (ANN), our collaborators investigated whether multiple candidate SNP can define genetic predisposition to asthma. In addition, new techniques have been introduced in collaboration with several national centres on the basis of transcriptome, proteome and other biological approaches to clarify functional validation of candidate SNP.

Lifestyle factors and IgE

It is widely acknowledged that the immune system is affected by environmental and lifestyle factors. In a large-scale industrial population, we performed a survey with which we were able to demonstrate that several comprehensive lifestyle factors, but not a single individual factor such as smoking, drinking or mental stress, played a significant role in controlling the key allergic molecule IgE (Table 3).[2] IgE levels are also dependent on a combination of multiple genetic variants, especially among the IL-4 receptor and its signaling. Because there is no model available to explain the interaction between genetic and environmental factors, our model for IgE may provide a new tool for analysing the interaction between genetic and environmental factors.

Association of lifestyle with a high risk of hyperimmunity and immunosuppression mediated by IgE

To test the hypothesis that the increase in allergic prevalence is related not only to environmental allergens, but also to comprehensive lifestyle, we administered a questionnaire to 733 workers at a hard metal plant that included 17 physical and mental health practices.[3] We have shown that eight practices are associated with increases or decreases of total and specific IgE levels, serving to keep them within the normal range (5–400 IU/mL), after controlling for age, sex and environmental factors. A significant ($P < 0.05$) trend for IgE to increase with a higher Health Practice Index in Allergic Reaction (HPIA)[6] category was found within age astrata, whereas an age-related decline (total) or increase (specific) in IgE level was found after controlling for HPIA (Fig. 1).[3]

Further confirmation of the definite effect of lifestyle on allergic reactions comes from higher heritability among younger pairs of identical twins of total IgE levels and

Table 2 Final 37 candidate single nucleotide polymorphisms for asthma

JSNP	Phenotype	*P*
IMS-JSTNo		0.0020
IMS-JSTNo	Childhood BA	0.0013
	Childhood BA with higher IgE	0.00069
	Severe childhood BA	0.00059
	Childhood BA with mite IgE+	0.00092
	Childhood BA onset < 3 years	0.0035
	Childhood BA treated with BDP	0.00081
IMS-JSTNo	Childhood BA	0.0014
	Childhood BA with higher IgE	0.00057
	Severe childhood BA	0.0010
	Childhood BA with AD	0.0017
	Childhood BA with mite IgE+	0.00074
	Childhood BA onset < 3 years	0.0024
	Childhood BA treated with BDP	0.0014
IMS-JSTNo	Childhood BA	0.0015
	Childhood BA with higher IgE	0.0022
	Severe childhood BA	0.00071
	Childhood BA with AD	0.0048
	Childhood BA with mite IgE+	0.0034
	Childhood BA treated with BDP	0.00086
IMS-JSTNo	Childhood BA with higher IgE	0.0074
IMS-JSTNo	Adult BA	0.00014
	Childhood BA with mite IgE+	0.0077
	Adult BA with higher IgE	0.000052
	Severe adult BA	0.00062
IMS-JSTNo	Childhood BA with higher IgE	0.0024
IMS-JSTNo	Childhood BA	0.0065
	Childhood BA with mite IgE+	0.0085
	Childhood BA onset < 3 years	0.00023
IMS-JSTNo	Childhood BA	0.0077
	Childhood BA with mite IgE+	0.0058
	Childhood BA onset < 3 years	0.00035
IMS-JSTNo	Childhood BA onset < 3 years	0.00054
IMS-JSTNo	Childhood BA with AD	0.0018
	Childhood BA onset < 3 years	0.0057
IMS-JSTNo	Childhood BA	0.0083
	Childhood BA onset < 3 years	0.0018
IMS-JSTNo	Childhood BA with AD	0.0024
	Adult BA with nasal polyp	0.0065
IMS-JSTNo	Childhood non-atopic BA	0.0020
IMS-JSTNo	Childhood BA treated with BDP	0.0024
IMS-JSTNo	Childhood BA	0.0040
	Childhood BA with mite IgE+	0.0012
	Adult BA with history of child BA	0.0035
IMS-JSTNo	Childhood BA	0.0051
	Childhood BA with mite IgE+	0.0015
	Adult BA with history of child BA	0.0039
IMS-JSTNo	Childhood BA	0.0083
	Childhood BA with AD	0.0065
	Childhood BA with mite IgE+	0.0064
	Childhood BA treated with BDP	0.00095
IMS-JSTNo	Severe adult BA	0.0026
IMS-JSTNo	Severe childhood BA	0.0018
	Childhood BA treated with BDP	0.0010
IMS-JSTNo	Childhood BA	0.0018
	Childhood BA with higher IgE	0.0092
	Severe childhood BA	0.0034
	Childhood BA with AD	0.0058
	Childhood BA with mite IgE+	0.0070
	Childhood BA onset < 3 years	0.0048
	Childhood BA treated with BDP	0.0034
IMS-JSTNo	Childhood BA	0.0072
	Childhood BA with higher IgE	0.0033
	Childhood BA with AD	0.0022
	Childhood BA onset < 3 years	0.00103
IMS-JSTNo	Childhood BA with higher IgE	0.00061
IMS-JSTNo	Childhood non-atopic BA	0.0050
IMS-JSTNo	Adult BA	0.0036
	Severe adult BA	0.0026
	Adult BA with AIA	0.0099
IMS-JSTNo	Childhood BA	0.0070
	Adult BA	0.00070
	Childhood BA treated with BDP	0.0097
	Adult BA with higher IgE	0.0070
	Severe adult BA	0.0029
IMS-JSTNo	Adult BA	0.0082
IMS-JSTNo	Childhood BA	0.0057
	Adult BA	0.00069
	Childhood BA with higher IgE	0.0039
	Severe childhood BA	0.0089
	Childhood BA treated with BDP	0.0085
	Adult BA with higher IgE	0.0060
	Severe adult BA	0.0040
IMS-JSTNo	Adult BA	0.0030
	Severe adult BA	0.0073
IMS-JSTNo	Adult BA with higher IgE	0.0024
IMS-JSTNo	Childhood BA	0.0061
	Adult BA	0.0021
	Childhood BA with higher IgE	0.010
	Severe childhood BA	0.0084
	Childhood BA treated with BDP	0.0079
	Severe adult BA	0.0077
IMS-JSTNo	Adult BA	0.0090
IMS-JSTNo	Childhood BA with higher IgE	0.0021
IMS-JSTNo	Severe adult BA	0.0065
IMS-JSTNo	Adult BA	0.00074
	Childhood BA treated with BDP	0.0084
	Severe adult BA	0.0041
IMS-JSTNo	Childhood BA with higher IgE	0.0045
IMS-JSTNo	Adult BA with AIA	0.0063

JSNP, a database of Japanese single nucleotide polymorphisms; BA, bronchial asthma; BDP, beclamethasane diproprionate; AD, atopic dermatitis; AIA, aspirin-induced asthma.

Table 3 Risk of elevated cord blood IgE and maternal IgE related to mother's age, frequency of birth, gender of baby, maternal lifestyles, diet and environment factors[2]

	Risk factor	Relative risk			
		Cord blood IgE (> 1.0 IU/mL)	Cord blood IgE (> 3.0 IU/mL)	Cord blood IgE (> 3.0 IU/mL) + high-risk mother[a]	Maternal IgE (> 400 IU/mL)
Frequency of birth	≤ 1	2.4 (1.5–4.6)[b]	3.3 (1.4–5.2)[b]	2.5 (1.2–4.9)[b]	1.6 (1.1–2.3)[c]
Age of mother	> 35 years	2.9 (1.8–5.0)[b]	2.8 (1.3–5.0)[b]		1.9 (1.2–3.3)[c]
Gender of baby	Boy	2.4 (1.2–4.8)[b]	3.0 (1.5–5.0)[b]	3.8 (2.0–5.8)[b]	ND
Positive allergic history for	Mother	2.8 (1.4–4.9)[b]	ND	1.8 (1.0–2.2)[b]	2.9 (1.7–4.8)[c]
	Father	1.3 (1.0–2.0)[c]			
	Grandpa				1.3 (1.0–1.9)[b]
	Siblings	1.4 (1.0–2.4)	2.5 (1.5–4.1)[b]	2.5 (1.6–4.0)[c]	1.3 (1.4–2.0)[b]
Maternal IgE	> 400 IU/mL	2.8 (1.2–4.8)[b]	ND	1.6 (1.0–2.2)[c]	ND
Diet					
Milk	Every day	1.0 (0.3–2.0)	1.1 (0.5–2.2)	1.0 (0.4–2.0)	
	> 3.5 L/day	1.2 (0.3–2.5)	1.2 (0.3–2.5)	1.1 (0.3–2.2)	
Eggs	Every day	1.1 (0.3–2.2)	1.1 (0.5–2.3)	1.0 (0.8–1.9)	
	> 3 every day	1.0 (0.3–2.0)	1.1 (0.5–1.0)	0.9 (0.4–2.0)	
Milk + eggs	Every day	1.1 (0.4–2.3)	1.3 (1.0–2.0)[b]	0.9 (0.3–1.9)	
Tofu	Every day	1.6 (1.0–2.2)[c]			
Soya beans	Every day	2.8 (1.3–5.0)[b]		2.8 (1.2–4.6)[b]	3.8 (2.2–5.4)[b]
Radishes	Every day	0.2 (0.1–0.5)[b]			
Orange/pear	Every day	0.3 (0.2–0.6)[b]		0.3 (0.2–0.6)[b]	
Peanuts	≥ 3/week			1.8 (1.1–2.4)[b]	1.8 (1.2–2.3)[c]
Lifestyle					
Regularity	Irregular	2.4 (1.2–4.4)[b]	2.8 (1.2–5.4)[b]	2.6 (1.1–4.6)[b]	
Physical exercise	< 1/week	2.5 (1.2–4.9)[b]	3.0 (1.3–5.5)[b]		
Smoking habits	Present/past	1.3 (1.0–1.8)[c]			
Sleeping pattern	≤ 6 h			1.4 (1.0–2.0)[c]	2.5 (1.0–4.4)[c]
Coffee, tea	≥ 5 cups/day			0.7 (0.5–0.9)[c]	
Life satisfaction	Good			1.2 (1.0–1.4)[c]	
HPIA	Low	2.1 (1.1–4.4)[c]	2.4 (1.1–4.3)[b]	1.8 (0.4–2.6)[c]	2.1 (1.1–3.5)[c]
Environmental					
House type	Modern	1.9 (1.0–2.5)[c]	3.3 (1.3–5.0)[b]	2.9 (1.3–4.8)[b]	
Facing large road	Yes		1.2 (1.0–1.6)[b]		
Carpets in home	Yes	3.3 (1.5–5.0)[b]		1.2 (1.0–2.1)[c]	1.6 (1.0–2.2)[c]
Animals in home	Yes			1.8 (1.0–2.4)[c]	1.8 (1.2–2.3)[c]

Multiple logistic analysis. Only factors with significant relative risk, except for exposure to eggs and milk, are listed.

Relative risk, odds ratio between high- and low-risk categories.

[a]With high IgE (> 400 IU/mL) and/or positive allergic history.

[b]$P < 0.01$ on the basis of Chi-squared test; [c]$P < 0.05$.

HPIA, Health Practice Index in Allergic Reaction.[6]

allergic disorders than among older pairs of identical twins. A marked synergism was found between undesirable lifestyle factors such as bipolar high-risk factors for the development of allergic diseases and immunosuppression characterized by low natural killer (NK) cell activity, through which levels of the soluble low-affinity IgE receptor are kept low.[3] Therefore, an effort to practice 'desirable' lifestyles may be of benefit in reducing the risk of immunoallergic disorders.

To examine the cumulative effect of lifestyle on allergic disorders, we investigated allergy discordance in monozygotic twin (MZT) pairs, as shown in Table 4.[3] The twin pairs were divided according to their allergic concordance into the following three groups: (i) both positive for allergy histories; (ii) only one positive; and (iii) neither positive. In the MZT pairs, there was an apparent gradient between HPIA score, IgE levels and allergic symptoms (Table 4).[3] Pairs with both twins having positive allergy

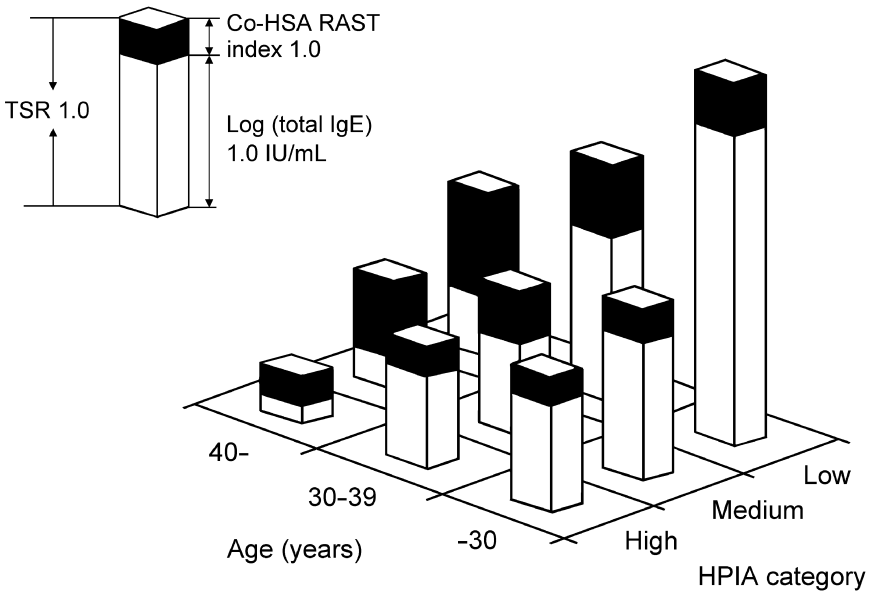

Fig. 1 Cummulative impacts of eight health practices in the Health Practice Index in Allergic Reaction (HPIA)[6] on log (total IgE levels) and cobalt-specific IgE in male subjects with exposure to hard metal dust. The three categories are low (0–4), medium (5,6) and high (7,8) HPIA scores. After controlling for age, the increases in total and specific IgE levels were significant ($P < 0.05$) between the high and low HPIA categories. In addition, there were significant ($P < 0.05$) trends for IgE to decrease (total) or increase (specific) with age, except for members of the low HPIA category.[3]

Table 4 Association of allergic symptoms and Health Practice Index in Allergic Reaction (HPIA)[6] score in monozygotic twins*

Reference	Allergy	No. pairs	Age (years)	Geometric mean IgE (IU/mL)	Intrapair correlation coefficient for IgE	Mean HPIA
Shirakawa *et al*.[3] (all males)	Both	13	64.6 ± 6.3	138.5[a]		5.88 ± 0.88[a]
	Either					
	+	26	62.3 ± 3.6	122.5[a,b]		
	–	26	62.3 ± 3.6	48.9		4.53 ± 0.85
	Neither	22	61.6 ± 3.6	44.5		4.60 ± 0.78
	Total	61 (33.3%)	62.8 ± 4.5	66.5	0.26	
Hopp *et al*.[12]	Both	22				
	Either	9	6–31	42.1		
	Neither	30				
	Total	61 (71.0%)			0.82	
Svartengren *et al*.[13]	Either (asthma)					
	+	9	30–49	60.5	–0.015	
	–	9	30–49	27.2	–0.015	
Edfors–Lubs[7]		2434 (24.4%)	35–75			

*Note that discordance of allergic prevalence and/or total IgE levels is associated with age difference in populations studied.

[a]$P < 0.05$ compared with neither twin having symptoms; [b]$P < 0.05$ compared with one of the twins without symptoms.

histories had a significantly ($P < 0.05$) higer mean HPIA score (5.88 ± 0.88) than pairs with both having negative allergy histories (4.60 ± 0.78). Among the pairs with one twin positive, the person with a positive history of allergy showed a significantly ($P < 0.05$) higher mean HPIA score (5.67 ± 0.88) than the person without a positive history (4.53 ± 0.85). These findings suggest that discordance of lifestyle between pairs may cause discordance of total IgE levels, which is responsible for discordance of allergic symptoms.[7]

Hygiene hypothesis

Allergy is a disorder of the immune system, but the prime function of the immune system is to protect the body from harmful infectious agents. Consequently, the question arises whether patterns of exposure to infectious agents can influence the risk of allergy. It is clear that the recent rapid rise in atopic disease has been seen in 'developed' environments, where exposure to infectious agents in lungs and the intestine has fallen swiftly due to

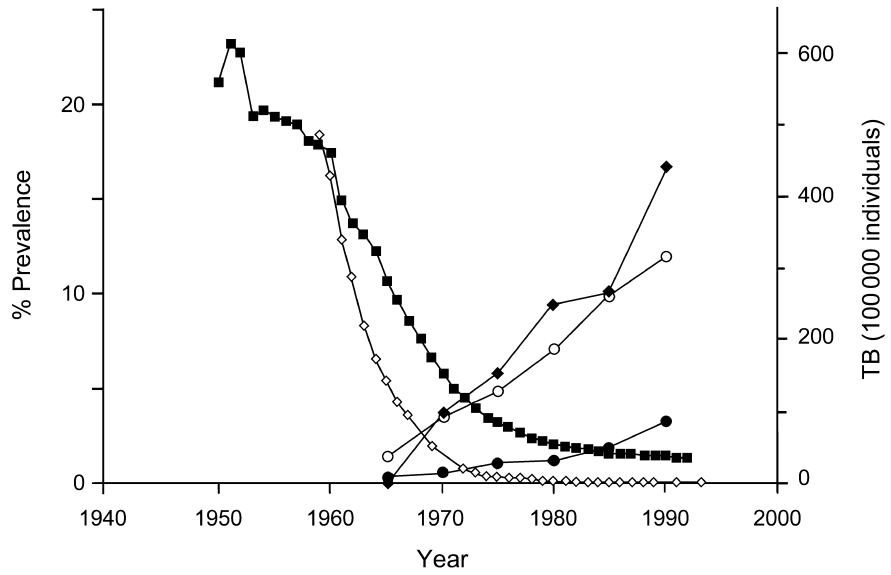

Fig. 2 Trends in the number of cases per 100 000 individuals of *Mycobacterium tuberculosis* (■) and of percentage prevalence of *Ascaris lumbricoides* (◇) infections and of atopic disorders (◆, rhinitus; ○, eczema; ●, asthma) in the past 50 years in Japan. TB, tuberculosis.[4] (Data taken from Ministry of Health and Welfare[8] and Itoh.[9])

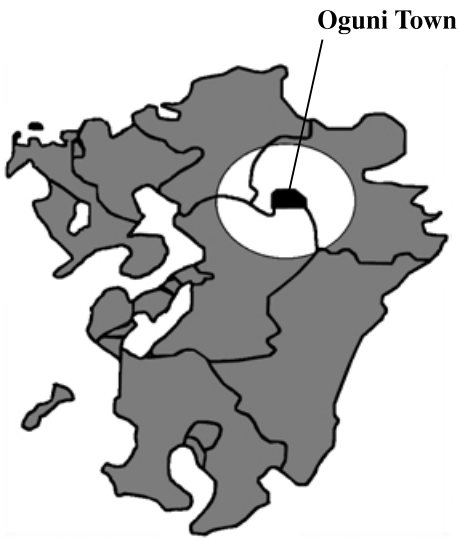

Fig. 3 Location of Oguni Town, Aso Gun, Kumamoto Prefecture.

improved hygiene (Fig. 2).[4,8,9] This is called the 'hygiene hypothesis'.

We have shown, in a large population of children from Wakayama, that exposure to the tuberculosis microrganisms in early life very strongly predicts less allergy and asthma in later childhood (Table 5).[5] We proposed that such infections in early life program the immune system in a way that is antagonistic to the development of allergic disorders. Results of different investigations are given in Table 6. Our suggestion has been confirmed by other investigators, showing that tuberculosis organisms can prevent experimental allergy in mice. In addition, it is well known from recent epidemiological surveys[10,11] that early development of mucosal flora seems to be important in preventing the future development of atopy. However, it remains unknown how gut bacilli may interact with genes predisposing to allergy. Thus, it is necessary to develop a model to analyze the relationships between genetics and environmental factors and to develop a 'model' to clarify the effects of environmental factors. Our work may lead to the development of vaccines that could be tested for preventing allergy and asthma.

Future perspective: General population survey at Oguni Town

To verify our preventive strategy for allergic disorders, we did our best to organize a general population survey at Oguni Town, Kumamoto Prefecture, where our group investigates all inhabitants to collect information on genetic, environmental and lifestyle factors. We are now making a new model to integrate these factors and to predict the development of allergic disorders. The location of Oguni Town is shown in Fig. 3. On the basis of this model, we will develop a new preventive program there.

Table 5 History of infectious diseases, atopic symptoms, IgE levels and cytokine profiles in subjects grouped by tuberculin reactivity[5]

Measurement	Group 1 (n = 290)	Group 2 (n = 289)	Group 3 (n = 213)	Group 4 (n = 75)	Total[§] (n = 867)
Tuberculin response					
At 6 years	–	–	+	+	
At 12 years	–	+	+	–	
Positive antiviral immunity (%)					
Measles (history + vaccine)	83.4	87.2	84.5	81.3	84.3
Chicken pox (history + vaccine)	86.9	82.3	82.2	82.7	83.9
Mumps (history + vaccine)	62.8	60.9	60.1	57.3	61.0
No. with IgE to *Ascaris*	2	2	2	1	7
Symptoms (%)					
Atopy (past + present)	46.8	33.9‡‡	25.8‡‡	38.7	36.6
Atopy (present)	32.1	7.9‡‡‡	9.8‡‡‡	30.7	18.5
Asthma (past + present)	13.4	4.1‡‡	3.7‡‡	6.8	7.4
Rhinitis (past + present)	16.2	4.8‡‡	8.6‡	14.6	10.4
Eczema (past + present)	22.7	12.8‡‡	12.2‡‡	16.0	16.2
Geometric mean IgE (IU/mL)	208	149**	98***	178	154
Positive ASE (%)	55.8	43.9‡‡	41.8‡‡	53.3	48.2
Atopic (high IgE or positive ASE %)	65.5	54.0‡‡	49.2‡‡	61.3	57.3
Median cytokine level (pg/mL)					
IL-4	1.88	0.96†	0.92†	1.66	1.22 (10.2–UD)
IL-13	18.3	10.2†††	7.8†††	19.1	14.2 (45.6–UD)
IL-10	5.9	3.1††	2.9††	5.9	3.9 (10.2–UD)
IL-12	UD	UD	UD	UD	UD
IFN-γ	7.8	11.0††	13.2††	6.4	10.5 (23.2–UD)
Positive family history within three generations (%)	54.1	49.8	49.8	48.0	51.0
Mean BMI	21.1	22.0	21.9	21.2	21.6

**$P < 0.01$; ***$P < 0.001$ (Student's t-test); †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ (median test); ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$ (χ^2) all compared with group 1.

[§]Where possible, maximum and minimum values are given in parentheses.

ASE, allergen-specific IgE; UD, undetectable; IL, interleukin; IFN, interferon; BMI, body mass index.

Table 6 Results of studies following the study of Shirakawa *et al*.[5]

Reference	Country	Study population		Age (years)	Wheezing/asthma	Allergic disease
		Number	BCG			
von Hertzen *et al*.[14]	Finland	2324	1162	[¶]Adults	Direct (men)/Inverse (women)*	Inverse†
von Mutius *et al*.[15]	23 countries	235 477		13–14	Inverse‡	Inverse‡
Shirtcliffe *et al*.[16]	38 countries			6–7	Inverse‡	
Shirtcliffe *et al*.[16]	55 countries			13–14	Inverse‡	

[¶]With tuberculosis (TB): *persistant asthma more frequent in men with TB, less frequent in women with TB at <16 years of age.

†Only in women; ‡ecological analysis.

BCG, Bacillus Calmette–Guérin.

Throughout this study, we provided a new comprehensive model to make profound understanding of pathogenesis of allergic disorders by integrating ongoing genetic analysis with environmental and lifestyle factors and developed a preventive program, which may be available for other common diseases.

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