Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Vegetable oils	Case-control		*N*: 248		
	Cross-sectional			↑: 249 (women) *N*: 249 (men)	*N*: 249
Alcohol	Cohort		*N*: 251		
	Case-control		*N*: 8		
	Cross-sectional	*N*: 15			
Carbonated beverages	Cross-sectional	*N*: 252	*N*: 252	*N*: 252	
Deep-fried foods	Cross-sectional		↑: 71		
Hamburger	Cross-sectional	↑: 252	*N*: 252	*N*: 252	
Takeaways	Cross-sectional	*N*: 252	*N*: 252	*N*: 252	
Early introduction of cereal into children's diets (before age of 3 mo)	Case-control		↑: 47		
Intake of nutrients					
Carbohydrates	Case-control		*N*: 244		
Fiber	Case-control		*N*: 48		
Total protein	Case-control		*N*: 244		
Soy protein	Cross-sectional				*N*: 245
Total fat	Case-control		*N*: 248		
	Cross-sectional			*N*: 249	↑: 249
Calcium	Case-control		*N*: 48, 244		
Magnesium	Case-control		↓: 48		
			N: 244		
Iron	Case-control		*N*: 244		
Sodium	Case-control		↓: 48		
Zinc	Case-control		*N*: 244		
Yttrium	Case-control		*N*: 244		
Selenium	Case-control		*N*: 244		
Vitamin A	Case-control		↓: 244		
Vitamin D	Case-control		*N*: 244, 253 (supplementation)		
Vitamin E	Cohort	*N*: 254 (during pregnancy)		*N*: 254 (during pregnancy)	
	Case-control		↓: 48, 244		
Vitamin K	Case-control		*N*: 244		
Vitamin C	Cohort	↑: 254 (during pregnancy)		↑: 254 (during pregnancy)	
	Case-control		↓: 244		
			N: 48		
	Cross-sectional	*N*: 11	*N*: 10		
Thiamine	Case-control		*N*: 244		
Riboflavin	Case-control		*N*: 244		
Niacin	Case-control		*N*: 244		
Vitamin B6	Case-control		*N*: 244		
Vitamin B12	Case-control		*N*: 244		
Folic acid	Case-control		*N*: 244		
Antioxidant	Case-control		*N*: 84		
Catechins	Case-control		*N*: 255		
Flavones	Case-control		*N*: 255		
Flavonols	Case-control		*N*: 255		
Daidzein	Cross-sectional				↓: 245

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Genistein	Cross-sectional				↓: 245
Saturated fatty acids	Cross-sectional		↑: 256	*N*: 249	*N*: 249
Palmitic acid	Case-control		*N*: 248		
Stearic acid	Case-control		*N*: 248		
Monounsaturated fatty acids	Cross-sectional		↓: 256	*N*: 249	↑: 249
Palmitoleic acid	Case-control		*N*: 248	*N*: 249	*N*: 249
Oleic acid	Case-control	*N*: 257	*N*: 257		
			↑: 248		
	Cross-sectional			*N*: 249	↑: 249
Alpha-Linolenic acid	Case-control	*N*: 257	↑: 257		
			N: 248		
	Cross-sectional			↓: 249	↓: 258
					N: 249
Eicosapentaenoic acid	Case-control	*N*: 257	*N*: 248, 257		
	Cross-sectional				*N*: 258
Docosahexaenoic acid	Case-control		*N*: 248		
Linoleic acid	Case-control		*N*: 248		
	Cross-sectional			*N*: 249	*N*: 249, 258
Arachidonic acid	Case-control		*N*: 248		
	Cross-sectional			*N*: 249	*N*: 249, 258
Trans fatty acid	Cohort				
Polyunsaturated/ saturated ratio	Cross-sectional			*N*: 249	*N*: 249
n-6/n-3	Case-control	*N*: 257	↑: 84		
			N: 248, 257		
	Cross-sectional			↑: 249	*N*: 249
Linoleic acid/Alpha-Linolenic acid	Case-control	↓: 257	↓: 257		
	Cross-sectional			↑: 249	*N*: 249
Arachidonic acid/Linoleic acid	Case-control	↑: 257	↑: 257		
Lipids	Case-control		*N*: 244		
Breastfeeding					
Breastfeeding	Cohort	↓: 30, 31, 37 (wheeze; 3–13 y) *N*: 37 (wheeze; < 3 y)	↑: 37, 57 (breastfeeding at 3, 6, and 9 mo; partial breastfeeding at 9 and 12 mo), 193 ↓: 30, 40, 242 (without maternal atopy), 259 *N*: 57 (breastfeeding at 12 mo; partial breastfeeding at 3 and 6 mo), 242 (maternal atopy), 260	↑: 43, 261 (without parental allergies) *N*: 63, 83, 242, 261 (with parental allergies)	*N*: 76, 125 (hay fever and/or asthma)
	Case-control		↑: 84	*N*: 58	
	Cross-sectional	↓: 50	↓: 239	↑: 262	↓: 26
		N: 262, 263	*N*: 26, 93, 263	*N*: 26, 93, 239	*N*: 93, 239, 262
Formula feeding	Cohort				*N*: 125 (hay fever and/or asthma)
Measurements					
In breast milk					
n-3	Cohort		*N*: 264	*N*: 264	
Alpha-Linolenic acid	Cohort		*N*: 264	↓: 264	
Eicosapentaenoic acid	Cohort		*N*: 264	*N*: 264	
Docosahexaenoic acid	Cohort		↓: 264	*N*: 264	

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
n-6	Cohort		*N*: 264	*N*: 264	
Linoleic acid	Cohort		*N*: 264	*N*: 264	
Arachidonic acid	Cohort		*N*: 264	*N*: 264	
Trans fatty acid	Cohort		↓: 264	↓: 264	
n-6/n-3	Cohort		↑: 264	↑: 264	
Linoleoc acid/Alpha-Linolenic acid	Cohort		*N*: 264	*N*: 264	
Eicosapentaenoic acid/Arachidonic acid	Cohort		*N*: 264	*N*: 264	
In blood					
Selenium	Cross-sectional		*N*: 265 (serum)		
β-Carotene	Cross-sectional	*N*: 246 (plasma)	*N*: 265 (serum)		
Vitamin A	Cross-sectional	↑: 246 (plasma)			
Vitamin E	Cross-sectional	*N*: 246 (plasma)	*N*: 265 (serum)		
Vitamin C	Cross-sectional	*N*: 246 (plasma)	↓: 265 (serum)		
Saturated fatty acids	Cross-sectional		↓: 266 (plasma)		
Monounsaturated fatty acids	Cross-sectional		*N*: 266 (plasma)		
Oleic acid	Cross-sectional				*N*: 258 (red blood cell membranes)
Polyunsaturated fatty acids (PUFA)	Cross-sectional		*N*: 266 (plasma)		
n-3	Cross-sectional		*N*: 266 (plasma)		
Docosahexaenoic acid	Cross-sectional		*N*: 266 (plasma)		
a-Linolenic acid	Cross-sectional		↑: 266 (plasma: asthma)		
Eicosapentaenoic acid	Cross-sectional		*N*: 266 (plasma)		↓: 258 (red blood cell membranes)
n-6	Cross-sectional		*N*: 266 (plasma)		
Gamma-Linolenic acid	Cross-sectional		*N*: 266 (plasma)		
Eicosadienoic acid	Cross-sectional		↑: 266 (plasma: asthma, DD) *N*: 266 (plasma: current)		
Eicosatrienoic acid	Cross-sectional		↑: 266 (plasma)		
Docosapentaenoic acid	Cross-sectional		*N*: 266 (plasma)		
Linoleic acid	Case-control	↓: 257 (serum)	↓: 257 (serum)		
	Cross-sectional		*N*: 266 (plasma)		*N*: 258 (red blood cell membranes)
Arachidonic acid	Cohort				
	Case-control	↑: 257 (serum)	↑: 257 (serum)		
	Cross-sectional		*N*: 266 (plasma)		*N*: 258 (red blood cell membranes)
PUFA: 22:4 n-6	Cross-sectional		*N*: 266 (plasma)		
Trans fatty acid	Cross-sectional		*N*: 266 (plasma)		
n-6/n-3	Cross-sectional				*N*: 258 (red blood cell membranes)
Arachidonic acid/ eicosapentaenoic acid	Cross-sectional				↑: 258 (red blood cell membranes)

↑: significant positive association
↓: significant inverse association
N: not statistically significant
DD: Doctor-diagnosed
Numerals in columns indicate reference numbers.

spect to traditional Japanese food, a cross-sectional study observed that consumption of soy and isoflavones was significantly associated with a decreased prevalence of allergic rhinitis among Japanese pregnant women.[245]

Overall, epidemiological evidence on the association of food and nutrient intake and allergic disease was not sufficient to draw any conclusions.

BREASTFEEDING

Twenty-two studies were identified with investigation on whether breastfeeding practice was associated with allergic diseases. While several investigations showed a protective effect of breastfeeding on wheeze and asthma, others failed to show such a beneficial relationship. In several studies, positive associations between breastfeeding and asthma and atopic dermatitis were observed. One cohort study found that the duration of breastfeeding was inversely associated with the risk of asthma in children without a maternal history of atopic diseases: adjusted OR was 0.35 (95% CI: 0.18–0.66) in children exclusively breastfed 9 or more months in comparison with children who had never been breastfed.[242] On the other hand, another cohort study found an increased risk of atopic dermatitis associated with breastfeeding in children without a parental history of allergic diseases (adjusted OR for exclusive breastfeeding for at least 4 months compared with less than 4 months = 1.29, 95% CI: 1.06–1.55).[261] These results should be interpreted with caution. The main factor that may have induced bias is inherent in the breastfeeding practice itself, that is, it is the personal choice of mothers whether or not to breastfeed. This choice is subject to several influences, including previous knowledge of allergic diseases or allergic diseases in the family and perceived benefits of breastfeeding or not breastfeeding.

The beneficial influence of breastfeeding on allergic diseases may be attributed to several possible mechanisms. Breast milk stimulates intestinal colonization with specific bacterial flora. Gut colonization induces the production of Th1 cytokines, which counterbalances Th2 activity. On the other hand, a possible detriment is protection against infections that can be important stimuli for the development of allergic diseases. Breastfeeding might reduce the effect of bacteria on the immune system, so that the infant does not fully develop mature immune response mechanisms.[267]

The evidence is insufficient to infer a causal relationship between breastfeeding and allergic diseases. Further research is needed to achieve a greater understanding.

FAMILY HISTORY

A summary of the results of investigation of the association between a family history of allergy and allergic diseases in offspring is shown in Table 3. Most of the studies showed that allergic diseases were likely to have a strong genetic component. The increased risk seemed to be present no matter which type of allergic diseases were in family members. No study showed an inverse relation with the presence of a family history of allergic diseases. Atopic heredity may influence susceptibility to allergic diseases. This indicates a positive association of family history of allergies and allergic disorders with such conditions in offspring.

DISCUSSION

In the present paper, we reviewed 263 studies on the associations of various environmental factors with wheeze, asthma, atopic dermatitis, and allergic rhinitis. Because to our knowledge there has not been such an extensive review on a wide range of environmental factors in relation to allergic disorders, including dietary intake and family history, this report may be useful for future research on this area.

Although a number of reports addressed the effect of environmental factors on allergic diseases, evidence is conflicting. The wide variation in results among the many epidemiological studies may be attributed, at least in part, to the limitation of environmental measurements using indirect approaches or surrogates. In addition, interpretations of findings were limited because most were case-control studies or of a cross-sectional nature which could not infer a causal relationship. However, such investigations are quite useful and much less costly, take much less time, and are more suitable for hypothesis generation than other methodologies.

It is important to note that findings should be interpreted and applied with great caution. First, the exclusion of literature in languages other than English could have introduced publication bias. Second, cited studies used various defined diagnostic criteria (e.g. doctor-diagnosed asthma, self-reported asthma, and according to questionnaires filled out by parents). Variations in outcome based on a variety of such diagnostic criteria would result in discrepant results. Third, we summarized the results without differentiating the age of subjects. The impact of risk factors among children may be different from that among adults due to age-specific differences in immune maturation or other potentially antiallergic effects. Lastly, many epidemiological investigations in terms of allergic disorders were not included in this review because our review consisted of a search of one database (PubMed) using only one set of search terms, and we did not perform additional searches from reference lists of the articles that fulfilled our inclusion criteria. Moreover, a number of reports regarding relationships with outcomes such as atopy, results of skin prick test, serum IgE levels, and bronchial hyperresponsiveness were not taken into consideration

Table 3 Family history and allergic diseases

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Family history					
Asthma	Cohort	↑: 32	↑: 32, 135		
		N: 81			
	Case-control		↑: 6		
	Cross-sectional	↑: 18, 50, 55, 92	↑: 18, 19, 55, 136		
			N: 25	*N*: 27	
Atopy or allergy	Cohort	*N*: 81			
	Case-control	↑: 44 (among < 2 y)			
		N: 44 (among 2 – 12 y)			
	Cross-sectional	↑: 9	↑: 9 (ever), 136		*N*: 9
			N: 9 (DD)		
Asthma/allergy	Case-control		↑: 48		
Atopic dermatitis	Cross-sectional			↑: 27	
Allergic rhinitis	Cross-sectional			*N*: 27	
Chronic bronchitis emphysema	Cross-sectional			*N*: 27	
Household tuberculosis	Cross-sectional	*N*: 9	↑: 9		↑: 9 (current, ever)
			N: 9		*N*: 9, 9 (DD)
Parental history					
Allergy or atopy	Cohort		↑: 74, 118	↑: 43	↑: 125 (hay fever and/or asthma)
			N: 41		
	Case-control			↑: 61	
	Cross-sectional		↑: 24, 41, 136	↑: 24	↑: 24
					N: 29
Asthma	Case-control		↑: 61		↑: 61
	Cross-sectional	↑: 16	↑: 93, 136	*N*: 16, 93	*N*: 16
Asthma and/or allergies	Case-control		↑: 167		
	Cross-sectional		↑: 51		
Atopic dermatitis	Cross-sectional	*N*: 16		↑: 16, 28, 93	*N*: 16
Rhinitis or hayfever	Cohort				↑: 76
	Cross-sectional	*N*: 16	↑: 93	↑: 16	↑: 16
				N: 93	
Maternal history					
Allergy or atopy	Cohort	*N*: 30	↑: 30, 38	↑: 43	↑: 26
	Cross-sectional		*N*: 26	*N*: 26	
Asthma	Cohort	↑: 31, 186 (persistent and late onset wheezing)	↑: 39, 40, 259		
		N: 33, 56, 164 (transient wheezing)		*N*: 43	
	Case-control		↑: 46, 84, 167		
	Cross-sectional	↑: 9, 14, 17	↑: 9, 52, 132	↑: 16	↑: 9, 16
			N: 9, 14		
Atopic dermatitis	Cohort			↑: 43	
	Case-control		↑: 46		
	Cross-sectional	↑: 16		↑: 16, 93	↑: 16

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Rhinitis or hayfever	Cohort	*N*: 164		↑: 43	
	Case-control		*N*: 46		
	Cross-sectional	↑: 92		↑: 16, 93	↑: 16
		N: 16		*N*: 16	
Paternal history					
Allergy or atopy	Cohort	↑: 30	↑: 30 (ever)	↑: 43	
			N: 30 (current)		
	Case-control		*N*: 167		
Asthma	Cohort	*N*: 164	↑: 37	↑: 43	
	Case-control		↑: 46, 167		
	Cross-sectional		↑: 132		
Atopic dermatitis	Cohort			↑: 43	
	Case-control		*N*: 46		
	Cross-sectional			↑: 93	
Rhinitis or hayfever	Cohort	*N*: 164		↑: 43	
	Case-control		↑: 46		
	Cross-sectional	↑: 92			↑: 93
in siblings					
Asthma	Cross-sectional		↑: 93	↑: 93	
Atopic dermatitis	Cross-sectional			*N*: 93	
Rhinitis or hayfever	Cross-sectional		↑: 93		↑: 93

↑: significant positive association
↓: significant inverse association
N: not statistically significant
DD: Doctor-diagnosed
Numerals in columns indicate reference numbers.

in the present review.

On the basis of this review, it is clear that the data are insufficient to conclude an association between many environmental factors and allergic disorders. As most studies were conducted in Western countries, the application of these findings to people in other countries, including Japan, may not be appropriate. Further studies on the incidence of allergic diseases are required to conclude the relationship of environmental factors and allergic disease, taking into account the timing of the environmental exposure and genetic factors.

ACKNOWLEDGEMENTS

We thank Ms Yukari Hayashi for editorial and secretarial assistance. This study was supported by Health and Labour Sciences Research Grants, Research on Allergic Disease and Immunology from the Ministry of Health, Labour, and Welfare, Japan.

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Allergology International. 2008;57:39-56
DOI: 10.2332/allergolint.R-07-150

REVIEW ARTICLE

Genetic Susceptibility to Atopic Dermatitis

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ABSTRACT
Atopic dermatitis (AD) is a chronic inflammatory skin disorder with an increasing prevalence in industrialized countries. AD belongs to the group of allergic disorders that includes food allergy, allergic rhinitis, and asthma. A multifactorial background for AD has been suggested, with genetic as well as environmental factors influencing disease development. Recent breakthroughs in genetic methodology have greatly augmented our understanding of the contribution of genetics to susceptibility to AD. A candidate gene association study is a general approach to identify susceptibility genes. Fifty three candidate gene studies (50 genes) have identified 19 genes associated with AD risk in at least one study. Significant associations between single nucleotide polymorphisms (SNPs) in chemokines (chymase 1–1903A > G), cytokines (interleukin13 Arg144Gln), cytokine receptors (interleukin 4 receptor 1727 G > A) and SPINK 1258 G > A have been replicated in more than one studies. These SNPs may be promising for identifying at-risk individuals. SNPs, even those not strongly associated with AD, should be considered potentially important because AD is a common disease. Even a small increase in risk can translate to a large number of AD cases. Consortia and international collaborative studies, which may maximize study efficacy and overcome the limitations of individual studies, are needed to help further illuminate the complex landscape of AD risk and genetic variations.

KEY WORDS
atopic dermatitis, epidemiology, genetic polymorphism

INTRODUCTION

The atopic diseases, particularly atopic dermatitis, food allergy, asthma and hay fever, are among the most common chronic diseases. The prevalence of atopic diseases has increased to epidemic dimensions over the past decades. In industrialized countries, 25–30% of the population is affected. Atopic diseases are a major cause of illness and disability and represent an important public health issue accounting for a large proportion of health care spending. Atopic dermatitis (eczema) is a chronic inflammatory skin disease with onset typically in early childhood and is the most common chronic inflammatory skin disease in children in industrialized countries.[1] For example, the prevalence of atopic dermatitis among schoolchildren is 21.1% in Japan,[2] 17.2% in the US[3] and 15.6% in Northern European countries.[4] It is commonly the initial clinical manifestation of allergic disease, often preceding the onset of respiratory allergies.[5] Along with asthma and allergic rhinitis, atopic dermatitis is an important manifestation of atopy that is characterized by the formation of allergy antibodies (IgE) to environmental allergens. In developed countries, the prevalence of atopic dermatitis is approximately 15%, with a steady increase over the past decades.[6,7] While many environmental components have been studied for years, significant progress has been made only recently in identifying the genes responsible for susceptibility of atopic diseases. In order to identify susceptibility genes for AD, two general approaches, genome-wide screens and candidate gene association studies, have been used. In candidate gene association studies, variations in known genes whose biological functions implicate them in the pathophysiology are compared between unrelated cases and controls. Significantly higher frequencies of alleles at candidate loci in cases compared with controls may indicate a causal relationship between the marker allele and the disease. In general, association studies are easier to

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Received 8 July 2007.

Table 1 Candidate Genes for Atopic Dermatitis

Gene Symbol	Gene Name	Locus
Pattern Recognition Receptors		
CARD4 (NOD1)	caspase recruitment domain-containing protein 4	7p15-p14
CARD15 (NOD2)	caspase recruitment domain-containing protein 15	16q21
CD14	monocyte differentiation antigen CD14	5q31.1
MBL2	lectin, mannose-binding, soluble, 2	10q11.2-q21
TLR2	Toll-like receptor 2	4q32
TLR4	Toll-like receptor 4	9q32-q33
TLR6	Toll-like receptor 6	4p14
Chemokines and Associated Molecules		
CCL2 (MCP-1)	chemokine (C-C motif) lagand 2	17q11.2-q12
CCL5 (RANTES)	chemokine (C-C motif) ligand 5	17q11.2-q12
CCL11 (Eotaxin)	chemokine (C-C motif) ligand 11	17q21.1-q21.2
CCL17 (TARC)	chemokine (C-C motif) ligand 17	16q13
CCR3	chemokine (C-C motif) receptor 3	3p21.3
CCR4	chemokine (C-C motif) receptor 4	3p24
CMA1	chymase 1	14q11.2
Cytokines and Associated Molecules		
IL1RN	interleukin 1 receptor antagonist	2q14.2
IL1RL1 (ST2)	interleukin 1 receptor-like 1	2q11.2
IL1A	interleukin 1, alpha	2q14
IL1B	interleukin 1, beta	2q14
IL4	interleukin 4	5q31.1
IL4R	interleukin 4 receptor	16p12.1-p11.2
IL5	interleukin 5	5q31.1
IL6	interleukin 6	7q21
IL10	interleukin 10	1q31-q32
IL12B	interleukin 12, beta	5q31.1-q33.1
IL12RB1	interleukin 12 receptor, beta-1	19p13.1
IL13	interleukin 13	5q31
IL18	interleukin 18	11q22.2-q22.3
TGFβ1	transforming growth factor, beta-1	19q13.1
TNFα	tumor necrosis factor, alpha	6p21.3
GM-CSF (CSF2)	granulocyte-macrophage colony-stimulating factor 2	5q31.1
STAT6	signal transducer and activator of transcription 6	12q13
IFNγ	interferon, gamma	12q14
Antigen Presentation Molecules		
HLA-A	major histocompatibility complex, class I, A	6p21.3
HLA-B	major histocompatibility complex, class I, B	6p21.3
HLA-DMA	major histocompatibility complex, class II, DM alpha	6p21.3
HLA-DMB	major histocompatibility complex, class II, DM beta	6p21.3
PSMB8 (LMP7)	proteasome subunit, beta-type, 8	6p21.3
PSMB9 (LMP2)	proteasome subunit, beta-type, 9	6p21.3
TAP1	transporter, ATP-binding cassette, major histocompatibility complex, 1	6p21.3
TAP2	transporter, ATP-binding cassette, major histocompatibility complex, 2	6p21.3
Others		
CTLA4	cytotoxic T lymphocyte-associated 4	2q33
KLK7 (SCCE)	kallikrein 7	19q13.33
RUNX1 binding site between SLC9A3R1- NAT9	runt-related transcription factor1 binding site between solute carrier family 9, isoform 3 regulatory factor 1 and N-acetyltransferase 9	17q25
SPINK5	serine protease inhibitor, Kazal-type, 5	5q32
Drug-Metabolizing Enzymes		
GSTP1	glutathione s-transferase, pi	11q13
GSTM1	glutathione s-transferase, mu-1	1p13.3
GSTT1	glutathione s-transferase, theta-1	22q11.2
NAT2	N-acetyltransferase 2	8p23.1-p21.3

perform than genome-wide screens because they do not require the collection of family material. Genetic and environmental factors determine disease susceptibility[8] and twin studies indicate that the genetic contribution is substantial.[9] Research on genetic and environmental relationships is necessary for better understanding AD susceptibility.

The objective of this review paper is to review disease genes and to contribute to our understanding of how genetic variation causes atopic dermatitis.

METHODS

To evaluate candidate genes, we conducted MEDLINE, Current Contents and Web of Science searches of papers published before August 2006 using "atopic dermatitis (eczema)" and "polymorphism" as keywords. Additional articles were identified through the references cited in the first series of articles. Using the MEDLINE database, we identified 48 studies that provided information on atopic dermatitis occurrence associated with genetic polymorphisms. No additional articles through other databases were identified.

SNP ANALYSIS AND ATOPIC DERMATITIS (Tables 1, 2)

PATTERN-RECOGNITION RECEPTORS

The specificity of the adaptive immune response, which is mediated by T and B cells, occurs through somatic mutation and the selection of receptors that best recognize microbial antigens. In contrast, the innate immune response relies on evolutionary ancient germline-encoded receptors, pattern-recognition receptors. These receptors recognize highly conserved microbial structures, enabling the host to recognize a broad range of pathogens quickly, without the need for time-consuming somatic mutation.[10] These microbial structures, known as pathogen-assocaited molecular patterns, are generally essential for the survival of the microorganism and, as such, are immutable.

The ability of the innate immune system to distinguish between pathogens has been of considerable interest in the past few years, and recent discoveries have led to some fundamental breakthroughs, although much is still not understood. The discovery of the Toll-like receptors (TLRs), in particular, has given an insight into the mechanisms of intracellular signalling after microbial sensing and initiation of protective immune responses. Recent progress has revealed that innate immune responses are initiated by various TLRs.[11] TLRs comprise a family of proteins that enhance certain cytokine gene transcription in response to various pathogenic ligands and control acquired immune responses such as Th1 responses.[12,13] TLR4 is a receptor for lipopolysaccharide (LPS).[14,15] Recent studies on mouse[16-18] and human[19] mast cells suggest that LPS-induced activation is mediated through TLR4 expressed on mast cells. A protective role for mast cells in bacterial infection was first addressed in a bacterial peritonitis animal model, and infection is suggested to be mediated by the production of TNFα as a consequence of TLR4 activation.[20-22] More recently, LPS-induced production of inflammatory cytokines (IL-1β, TNF-α, IL-6, and IL-13) from mast cells in the peritoneal cavity and the resulting neutrophil recruitment have been suggested to be important for protection in septic peritonitis.[22] In addition, TNFα produced by mast cells is involved in hypertrophy of draining lymph nodes during intradermal bacterial infection.[23] However, the consequences of LPS-induced mast-cell activation in allergic airway inflammation are not well elucidated. Although the role of the non-TLR pattern-recognition receptors (CARD4, CARD15, CD14, MBL2) is generally less well-appreciated, it is becoming increasingly clear that these receptors also play key roles in initiating an innate immune response.

CARD4 (*NOD1*) maps on chromosome 7p15–p14. It covers 54.49 kb on the reverse strand. Eleven *CARD4* (*NOD1*) SNPs, such as rs2736726 (A > G), rs2075817 (A > G), rs2975632 (C > T), rs3030207 (A > G), rs2075818 (C > G), rs2235099 (C > T), rs2075821 (A > G), rs2075822 (C > T), rs2907749 (A > G), rs2907718 (C > T), rs5743368 (A > G), were investigated in a German population. Genotypes AA at rs2736726 and GG at rs2075817 were weakly protective for AD, with odds ratios (ORs) of 0.41 (95% CI = 0.18–0.94) and 0.43 (95% CI = 0.18–0.99), respectively.[24] It has been also observed that haplotype rs 2736726 A- rs2075817 G - rs2975632 T- rs3030207 A- rs2075818 C- rs2235099 C- rs2075821 G - rs2075822 T- rs2907749 A- rs2907718 C- rs5743368 G is weakly associated with atopic eczema (OR = 0.260, 95% CI = 0.07–0.92).[24]

CARD15 (*NOD2*) maps on chromosome 16q21. It covers 39.45 kb on the direct strand. No significant associations between AD and any SNP (2104C > T, 2722 G > C, 802T > C, 534 G > C, rs1077861 (intron 10A > T), 2863 G > A, 4278A > G, -60A > G) or haplotype of CARD15 were observed.[25] Associations of three SNPs (2104C > T, 2722 G > C and 3020iC) with AD in children have been reported. Children with the C allele of 2722 G > C SNP had a 1.85-fold risk (95% confidence interval (CI) = 1.10–3.13) of developing AD.[26]

CD14 maps on chromosome 5q22–q32. It covers 1.95 kb on the reverse strand. In a small study, children with the CT genotype of the *CD14*-159C > T SNP had a significantly lower prevalence (p = 0.017) of AD at three years of age compared with those with the genotypes CC and TT combined,[27] although the *CD14*-159C > T SNP was not associated with an increased risk of AD in German children.[28] No significant difference was found in the genotype frequencies of -159C > T, -1145 G > A, -1359 G > T and

Table 2 Polymorphisms of Candidate Genes for Atopic Dermatitis

Gene symbol	SNP	Ref.
Pattern-Recognition Receptors		
CARD4 (NOD1)	haplotype (rs2736726 (A>G), rs2075817 (A>G), rs2975632 (C>T), rs3030207 (A>G), rs2075818 (C > G), rs2235099 (C > T), rs2075821 (A > G), rs2075822 (C>T), rs2907749 (A>G), rs2907718 (C>T), rs5743368 (A>G))	24
CARD15 (NOD2)	− 60A > G, 534G > C, 802T > C, 2104C > T, 2722G > C, rs1077861 (intron10A > T), 2863G > A, 4278A > G, 3020iC	25, 26
CD14	− 1145G > A, − 1359G > T, − 550C > T, − 159C > T	27, 28, 29
MBL2	Gly54Asp	30
TLR2	rs5743708 (A > G), rs4696480 (T > A), rs3804099 (T > C), rs3804100 (T > C)	31, 32
TLR4	rs4986790 (A > G), rs4986791 (C > T), rs2770150 (T > C), rs6478317 (A > G), rs1927911 (C > T), rs2149356 (C > T), rs7873784 (G > C), rs1927906 (A > G)	31, 32
TLR6	rs5743810 (T > C)	33
Chemokines and Associated Molecules		
CCL2 (MCP-1)	− 2518A > G	63
CCL5 (RANTES)	− 403G > A, − 401G > A, − 28C > G	63, 64
CCL11 (Eotaxin)	− 426C > T, − 384A > G, 67G > A	67
CCL17 (TARC)	− 431C > T	71
CCR3	51T > C	75
CCR4	1014C > T	76
CMA1	− 1903A > G	77, 78, 79, 80, 81, 82
Cytokines and Associated Molecules		
IL1RN	penta-allelic 86-bp tandem repeat in intron 2	100
IL1RL1 (ST2)	−26999G>A, −27639A>G, 744C>A, 11147C>T, 2992C>T, 5283G>A, 5860C>A	101
IL1A	− 899T > C	102
IL1B	− 1418T > C, − 511T > C, 315T > C, 3953T > C	100,102, 103
IL4	− 590T > C, − 589C > T, 33T > C	104, 105, 106
IL4R	− 3112C > T, − 1803T > C, − 327C > A, − 326A > C, − 186G > A, 223C>G>T>A, 1199C>A, 1291C>T, 1242T>G, 1307T>C, 1507C > T, 1727G > A, 2356C > T	106, 107, 108, 109
IL5	− 703C > T	110
IL6	− 922A > G, − 174C > G	100, 102
IL10	−1117G>A, −1082G>A, −854C>T, −819T>C, −592A>C, −571C>A	100, 102, 106
IL12B	1188A > C, 4237G > A, 4496A > G, 4510G > A	106, 111
IL12RB1	− 111A > T, − 2C > T, 4443C > T, 5970G > C, 17183T > C, 17369C > T, 25748T > C, 27637A > T	112
IL13	− 1111C > T, − 1024C > T, 704A > C, 1103C > T, Arg144Gln, 1293C > T	102, 105, 106, 113, 114, 115
IL18	− 137G > C, − 133C > G, − 132A > G, 113T > G, 127C > T	116
TGFβ1	− 590C > T, 869C > T, 915G > C	102, 117
TNFα	− 1031T > C, − 863C > A, − 857C > T, − 308G > A, − 238G > A	100, 102, 103, 106
GM-CSF (CSF2)	− 1916T > C, − 677C > A, 3606T > C, 3928C > T	103, 119
STAT6	2964G > A, 13/14/15/16 GT repeat in exon 1, short tandem repeat in exon 1	106, 120
IFNγ	short tandem repeat in intron 1	106

(Continued)

Table 2 (Continued)

Gene symbol	SNP	Ref.
Antigen-Presentation Molecules		
HLA-A	1, 2, 3, 11, 24, 26, 29, 30, 31, 33, 66	130
HLA-B	7, 8, 13, 14, 16, 27, 35, 37, 38, 39, 46, 48, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 67, 71, 75	130
HLA-DMA	Val140Ile, Gly155Ala, Ile179Thr, 184Arg-His-Cys	131
HLA-DMB	144Ala-Glu-Val	131
PSMB8 (LMP7)	3911G > T, 3912C > T, 4069C > T	130
PSMB9 (LMP2)	Arg60His	130
TAP1	Val333Ile, Gly637Asp	130, 136
TAP2	Ile379Val, Thr565Ala, Ala665Thr, Gln687Stop	130
Others		
CTLA4	49A > G	159
KLK7 (SCCE)	AACC insertion	170
RUNX1 binding site between SLC9A3R1- NAT9	rs734232 (G > A)	171
SPINK5	IVS12 − 26C > T, IVS12 − 10A > G, IVS14 + 19G > A, IVS13 − 50G > A, 1103A > G, 1156G > A, 1188T > C, 1258G > A, Asp106Asn, Gly463Gly, Val553Val, Leu756Leu, Gly804Gly	173, 174 175 (175),176, 177
Drug-Metabolizing Enzymes		
GSTP1	1404A > G, 2294C > T	189
GSTM1	Deletion polymorphism (non-null or null genotype)	189
GSTT1	Deletion polymorphism (non-null or null genotype)	189
NAT2	481C > T, 590G > A, 857G > A	195, 196

Disease susceptible SNPs found to be significant in one study and the corresponding references are single-underlined.
Disease susceptible SNPs found to be significant at least in two independent studies and the corresponding references are double-underlined.

-550C > T SNPs between AD patients and controls.[29]

MBL2 maps on chromosome 10q11.2–q21. It covers 6.32 kb on the reverse strand. Recently, three variants at codons 52, 54, and 57 of exon 1 of the *MBL2* gene have been identified. The *MBL2* Gly54 Asp SNP was not associated with an increased risk of AD in a Japanese population.[30]

TLR2, *TLR4* and *TLR6* map on chromosome 4q32, 9q32–q33 and 4p14, respectively. In a German population, the *TLR2* rs5743708 (A > G) SNP increases the susceptibility to severe AD while AD patients exhibit a higher frequency of the TLR4 polymorphisms rs4986790 (A > G) and rs4986791 (C > T) SNPs.[31] However, it has been found that common *TLR2* (rs4696480 (T > A), rs3804099 (T > C), rs3804100 (T > C), rs5713708 (G > A) or *TLR4* (rs2770150 (T > C), rs6478317 (A > G), rs1927911 (C > T), rs2149356 (C > T), rs4986790 (A > G), rs4986791 (C > T), rs7873784 (G > C), rs1927906 (A > G)) variants or haplotypes were not associated with an increased risk of AD in another German population.[32] There was no association between the *TLR6* rs5743810 (T > C) polymorphism and risk for AD.[33]

CHEMOKINES AND RELATED MOLECULES

Chemokines are a group of chemotactic cytokines that induce inflammatory cell mobilization through a concentration gradient.[34] Chemokines are relevant in allergy and asthma not only for their role in regulating leukocyte recruitment, but also for other activities, such as cellular activation, inflammatory mediator release, promotion of Th2 inflammatory responses, and regulation of IgE synthesis.[35] Chemokines are divided into four classes on the basis of their protein structure (specifically the location of cysteine motifs conserved within the N-terminal domain): CXC, CC, C, and CX3C chemokines. To date, over 50 chemokines have been identified, of which 28 are CC chemokines, 16 are CXC chemokines, two are C chemokines (XCL1 and XCL2) and one is a CX3C (CX3CL1) chemokine.[36] The CC and CXC chemokines are inflammatory chemokines while the C and CX3C chemokines are immune chemokines. The chemokines discussed in the remainder of the paper are CC chemokines. Some chemokines, such as CCL5 (RANTES), CCL11 (eotaxin), CCL2 (MCP-1),

CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP-4) and macrophage inflammatory protein (MIP)-1α/CCL3, cause cellular activation and inflammatory mediator release by basophils and eosinophils.[35] Receptors CCR1 through CCR10 bind the CC chemokine; receptors CXCR1 through CXCR6 bind CXC chemokines; and C and CX3C chemokines bind to XCR1 and CX3CR1, respectively.[36] At least three chemokine receptors have been shown to mediate the recruitment of Th2 cells: CCR3, the receptor for CCL5 (RANTES), CCL11 (eotaxin), CCL2 (MCP-1), and CCL13 (MCP-4), which is also expressed on eosinophils and basophils;[37-39] CCR4, the receptor for CCL17 (TARC) and CCL22 (MDC); [40,41] and CCR8, the receptor for CCL1 (I-309).[42,43]

CCL5 (RANTES) has several functions, including the stimulation of histamine secretion from basophils, the activation of eosinophils, and the mobilization of monocytes, eosinophils, and memory T_H cells (with a preference for $CD45RO^+$ and $CD4^+$ subtypes). Although virtually all nucleated blood and tissue cells produce chemokines, the primary source of cutaneous CCL5 (RANTES) appears to be dermal fibroblasts. CCL11 (eotaxin 1) is a selective chemoattractant and activator of both eosinophils[44] and TH_2 lymphocytes, and it might also operate as an indirect negative regulator of neutrophil recruitment.[45,46] Enhanced levels of both CCL5 (RANTES) and CCL11 (eotaxin 1) have been identified in the sera of patients with AD,[47] with CCL5 (RANTES) demonstrating a significant positive correlation with both total serum IgE levels and eosinophil numbers. Eotaxin 1 also demonstrates a significantly increased pattern of gene expression in lesional skin biopsy specimens taken from patients with AD compared with those from nonatopic control subjects.[48] Consistent with a role for these CC chemokines in the pathology of AD, tacrolimus (FK506) ointment, a clinically effective macrolide lactone AD treatment, has been shown to suppress the expression of both CCL5 (RANTES) and CCL11 (eotaxin 1) in lesional AD skin.[49] UV-B irradiation, used in phototherapy, also inhibits cytokine-stimulated CCL5 (RANTES) expression in cultured epidermal keratinocytes.[50] Together these data indicate that CC chemokines, particularly CCL5 (RANTES) and CCL11 (eotaxin 1), might represent useful future targets for the genetic dissection of AD.

CCL17 (TARC) is predominantly expressed on Th2 lymphocytes, basophils, and natural killer cells.[51-54] Thus, CCL17 is likely to play an important role in Th2-type immune responses by selectively recruiting $CCR4^+$ Th2-polarized memory/effector T cells into inflamed tissues. Cutaneous lymphocyte-associated antigen (CLA) is expressed by the vast majority of skin-infiltrating T cells and is involved in the recruitment of skin-associated T cells to inflammatory sites by interacting with the endothelial cell ligand E-selectin, which is highly expressed in inflamed skin.[55] Essentially all CLA^+ skin-seeking memory effector T cells express CCR4.[56,57]

Mast cell chymase (CMA1) is a glycosylated chymotryptic-like serine protease that is found at high levels in the secretory granules of mast cells and appears to operate in concert with histamine and tryptase to confer a range of proinflammatory effects upon release from activated cells.[58,59] It activates several biological mediators, including angiotensin I, IL-1β, and endothelin-1, by the cleavage of precursor forms of these molecules.[60] The mechanism of chemokine production by endothelial cells stimulated with mast cell tryptase is unclear. One possible mechanism involves activation of protease-activated receptors (PARs). Tryptase or thrombin cleaves the amino-terminal extracellular extension of the intact and inactivated receptor, exposing the amino terminus, which then functions as a receptor agonist, binding to a region of the receptor and activating it. Four subtypes of PAR have been cloned. The thrombin receptor-1 (PAR-1) is expressed on endothelial cells but does not appear to be activated by tryptase. PAR-2 is also expressed on endothelial cells, and it may be activated by tryptase.[61] The effect of human mast cell tryptase on endothelial cells inducing the production of chemokine may be mediated by this receptor. PAR-3 and PAR-4 can also be cleaved by thrombin.[62] However, little is known about the relationship between tryptase and these receptors.

CC cytokine genes cluster on the q-arm of chromosome 17. The *CCL2 (MCP-1)* -2518A > G SNP has not been shown to be associated with AD in a Hungarian cohort.[63]

CCL5 (RANTES) maps on chromosome 17q11.2–q12. It covers 9.01 kb on the reverse strand. Two polymorphisms in the *CCL5 (RANTES)* promoter region (-28C/G and -403 G/A) affect the transcription of the *CCL5 (RANTES)* gene.[64,65] In human cell lines, the -28 G allele of -28C > G SNP and the -403 A allele of -403 G > A SNP increase promoter activity of *CCL 5 (RANTES)* compared to the more frequent -28C allele and the -403 G allele, respectively, suggesting that these polymorphisms increase *CCL5 (RANTES)* expression in humans.[64] In fact, these variations result in the generation of a novel consensus binding site for the GATA transcription factor family and has been associated with enhanced *CCL5 (RANTES)* production in patients with AD.[66] The -401A allele of the -401 G > A SNP was more frequent in AD patients compared with control subjects in a German population ($p < 0.037$).[64] There was no association between -28C > G and -403 G > A SNPs in the *RANTES* promoter, and -2518A > G SNP in the distal regulatory region of the gene and AD in a Hungarian population.[63]

CCL11 (eotaxin 1) maps on chromosome 17q21.1–q21.2. It covers 2.66 kb on the direct strand. A number of polymorphisms have been identified in the gene. Although the two SNPs (-426C > T, -384A > G)