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

388

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.

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334

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338

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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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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 me-

diated 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,	173, 174
	1103A > G, 1156G > A, 1188T > C, 1258G > A,	175 (175),176,
	Asp106Asn, Gly463Gly, Val553Val, Leu756Leu, Gly804Gly	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),

344

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 Tн 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 TH2 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] Essen-

tially 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)

345

in the promoter region of the *CCL11* gene were associated with serum IgE levels in AD patients, the two and 67 G > A SNPs were not shown to be associated with susceptibility to AD.[67] This apparent specificity of this effect might be related to the diminutive size of the genotyped sample of this single study,[67] the low magnitude of the underlying genetic effect, and the power advantage associated with the use of quantitative traits. Consequently, these data require replication, as well as further study in a more substantial cohort of subjects. An orally available antagonist of the eotaxin 1 receptor (*YM-344031*) does, however, lend some support to the genetic findings because it has recently been shown to inhibit both immediate and late-phase antigen-induced cutaneous inflammation in a mouse model of allergy.[68] Significant linkage disequilibrium was observed between positions -426 and -384, and also between -384 and 67.[69]

The *CCL17* (*TARC*) maps on chromosome at 16q13. It covers 11.30 kb on the direct strand. The serum TARC levels of patients with AD were significantly elevated and correlated with disease activity, and immunoreactive TARC levels were detected in epidermal keratinocytes (KCs), dermal infiltrating cells, and endothelial cells in acute and chronic lesional skin.[70] These observations strongly suggest that KCs can be a source of TARC in the lesional skin of patients with AD and that KCs producing TARC may be involved in the pathogenesis of AD. Although some SNPs of *TARC* are candidates as a genetic factor in AD, no association between AD and the -431C > T SNP of the *TARC* gene was observed in a Japanese population.[71] The results of the study, however, should be considered very preliminary due to the small number of AD patients.

CCR3 maps on chromosome 3p21.3. It covers 143.70 kb on the direct strand. As stated earlier, CCR3 is a receptor for various chemokines which are important in the pathogenesis of AD. Therefore, the biological activities of *CCR3* suggest that polymorphisms of *CCR3* may impart an increased risk for AD. Several SNPs in *CCR3* have been reported, including silent mutations (51T > C[72,73] and 240C > T[73]) and missense mutations (652T > A,[74] 824 G > A,[72,73] 971T > C,[72] 1052T > C[73]). There was no significant difference in genotype frequencies of 51T > C SNP of the *CCR3* gene between AD patients and controls.[75]

CCR4 maps on chromosome 3p24. It covers 3.36 kb on the direct strand. There was no significant association with the 1014C > T SNP of the *CCR4* gene.[76]

CMA1 maps on chromosome 14q11.2. It covers 2.91 kb on the reverse strand. There have been several reports of a significant association between a *CMA1* promoter polymorphism (-1903A > G) and atopic eczema in Japanese adults and school-children.[77] These results could not be confirmed in another Japanese study with 100 patients and 69

patient-parents-trios[78] and an Italian study with 70 patients.[79] There was also no association between *CMA1*-1903A > G genotype and AD risk in Japanese but there was a significant association between the *CMA1* genotype and AD patients with a serum IgE concentration of < 500 IU/mL.[80] Recently, a family-based association study in Caucasians revealed a significant association of this polymorphism with total IgE levels in patients with self-reported AD.[81] As in the study of Mao et al.[77] a significant association between the *CMA1*-1903A > G polymorphism and AD was observed by Weidinger et al.[82] It may be speculated whether this DNA variant alters the expression of chymase. Recently, it has been shown that CMA1 is increased in chronic atopic eczema skin lesions,[83] and a potential role of chymase in the promotion of skin barrier defects and cutaneous neovascularization has been suggested.[84] Preliminary studies in animal models have indicated a therapeutic potential of chymase inhibitors in AD.[85,86]

Ma et al.[77] suggested that variants of *CMA1* may have been one source of genetic risk for AD in a Japanese population while other Japanese studies[78,80] failed to confirm this association. Functional studies and analyses of other loci are needed to clarify the consequences of the -1903A > G polymorphism in the *CMA1* gene and might determine whether chymase will qualify as a target for therapeutic interventions in AD.

CYTOKINES

Cytokines have been functionally divided into two subgroups: Th1 cytokines, mainly interleukin (IL) 2, IL12, interferon (IFN)γ, and tumor necrosis factor (TNF)α, which activate the cellular machinery of the immune system; and Th2 (IL4, IL5, IL6, IL10 and IL13) cytokines, which activate the humoral machinery.[87-90] Unusual deviation of the balance between Th1 and Th2 results in many immune diseases such as allergy and autoimmune diseases. Excessive Th1 immune response has been implicated in autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, liver injury and graft versus host disease while unusual deviation in Th2 immunity causes allergic diseases and systemic lupus erythematosus.

For example, IL2, mainly secreted by Th1 cells, is an autocrine stimulator of Th1 cell differentiation and proliferation resulting in a T cell shift towards the Th1 phenotype. IL12 is a proinflammatory interleukin mainly produced by macrophages, B cells, and DCs. It promotes Th1 cell function while suppressing Th2 cell function. IFNγ can down-regulate allergic airway inflammation and mucus production,[91] further supporting the critical importance of Th2 cells in allergy and asthma. Of note, airway hyperresponsiveness (AHR) is induced by the transfer of IL-4-deficient Th2 cells, with a concomitant marked reduction of eosinophilia. This suggests that Th2 cells can induce AHR

346

even via IL4-independent mechanisms, but not by transfer of Th1 cells. In contrast, Th1 cells induced neutrophilic inflammation without AHR.[92] In another murine model of acute eosinophilic airway inflammation, however, Th1 cells were required in addition to Th2 cells for endogenous eosinophil recruitment, suggesting that Th2 cells may need Th1-derived signals for effective recruitment to airways.[93] Finally, engineering of Th2 cells to produce latent transforming growth factor (TGF) β1 reverted allergen-induced AHR and inflammation, which supports the concept that TGFβ-producing T cells play an important regulatory role in asthma,[94] and also that airway fibrosis and remodelling may be the final consequence of chronic or repeated TGF-β production. TNFα is expressed on the cell membrane and is then hydrolyzed to release the soluble form, which forms homotrimers. TNFβ (LT-α) has no cell membrane attachment domain but can form either membrane-anchored heterotrimers with LT-β or soluble homotrimers.

It is of note that Th2 cytokines can account directly or indirectly for the great majority of pathophysiological manifestations of allergic patients. IL4 is potentially pro-inflammatory and pro-atherogenic and induces circulating eosinophils to roll on and adhere to endothelial cells.[95] These eosinophils can then be attracted to target tissues by both IL-5 and chemokines. IL10 is a prototype anti-inflammatory interleukin produced mainly by activated T cells, B cells, and macrophages. It was described in mice as a Th2 cytokine that selectively inhibits IFNγ and granulocyte-macrophage colony-stimulating factor 2 (GM-CSF or CSF2) production by the Th1 cells. IL-13 is responsible for mucus hypersecretion by mucus cells, and induces metaplasia of mucus cells.[96] IL4 and IL13 stimulate fibroblast growth and chemotaxis, as well as the synthesis of extracellular matrix proteins.[97,98] However, subepithelial fibrosis in asthma also results from the activity of TGFβ, produced by T cells, eosinophils and fibroblasts, as well as of IL-6 produced by several cell types, including Th2 cells themselves.[99] Taken together, these findings indicate that Th2 cytokines, either directly or indirectly, can account for the hallmarks of allergic inflammation.

IL1RN maps on chromosome 2q14.2. It covers 34.70 kb on the direct strand. The polymorphism in intron 2 of the *IL1RN* gene is caused by a variable copy number of an 86-bp sequence. The 4-repeat (*IL1RN*1) and 2-repeat (*IL1RN*2) alleles are most common, while the other alleles occur at a combined frequency of less than 5%. No association was found between the variable number of tandem repeat polymorphisms in intron 2 of the *IL1RN* gene and AD.[100]

IL1RL1 (*ST2*) maps on chromosome 2q12. It covers 40.54 kb on the direct strand. A significant association between AD and the -26999G > A SNP of the ST2 gene was found in a Japanese population (OR = 1.86, 95% CI = 1.42–2.45).[101] On the other hand,

2992C > T, 5283G > A, 5860C > A, 11147C > T, 744C > A and -27639A > G SNPs were not associated with AD risk.[101]

IL1A and *IL1B* map on chromosome 2q14. The former covers 11.48 kb on the reverse strand and the latter covers 7.16 kb on the reverse strand. The -899T > C SNP of the *IL1A* gene was not associated with AD risk.[102] No association was found between either the -511C > T, 3953T > C, 3953T > C, -1418T > C or the 315T > C SNPs of the *IL1B* gene and AD.[100,102,103]

IL4 maps on chromosome 5q31.1. It covers 9.01 kb on the direct strand. The T allele of -590T > C SNP was associated with an increased risk of AD in a Japanese population.[104] In Caucasians the T allele of IL4 -589C > T SNP was significantly associated with the development of AD at 24 months of age.[105] No association between SNPs (-590T > C and 33T > C) of *IL4* and AD was found in a Chinese population.[106]

IL4R maps on chromosome 16p11.2–12.1. It covers 50.86 kb on the direct strand. Many SNPs (-3112C > T, -1803T > C, -327C > A, -326A > C and -186G > A) or haplotypes (α) of the *IL4R* gene are associated with AD.[107] Seven SNPs (223C > G > T > A, 1199C > A, 1291C > T, 1307T > C, 1727G > A, 2356C > T) and a silent 1242T > G have been demonstrated to have functional significance. Caucasian children with the rare homozygous 1727G > A polymorphism had a higher prevalence of flexural eczema in the first 6 months compared with the heterozygote and the wild type homozygote genotypes combined.[108] It has been demonstrated that the 1727G > A SNP was significantly associated with AD in another Japanese population.[109] No association between SNPs (1199C > A, 1242T > G, 1507C > T and 1727G > A) of *IL4R* and AD was found in a Chinese population, however.[106]

IL5 maps on chromosome 5q31.1. It covers 2.08 kb on the reverse strand. The -703C > T SNP of *IL5* was not significantly associated with AD in Japanese.[110]

IL6 maps on chromosome 7p21. It covers 6.12 kb on the direct strand. No association was found between the -174C > G SNP of the *IL6* gene and AD.[100] Similarly, the -174C > G and -922A > G SNPs were not linked to AD.[102]

IL10 maps on chromosome 1q31–q32. It covers 4.89 kb on the reverse strand. The -1082A > G, -819T > C and -592A > C SNPs of the *IL10* gene did not contribute to the development of AD.[106] No association was found between AD and the -1082A > G SNP of the *IL10* gene.[100] Also, -571C > A, -854C > T and -1117G > A SNPs of the *IL10* gene were not associated with AD.[102]

IL12B maps on chromosome 5q31.1–q33.1. It covers 15.69 kb on the reverse strand. The AA genotype of *IL12B* 1188A > C SNP was associated with decreased risk of AD in a Japanese population (OR = 0.44, 95% CI = 0.20–0.95).[111] The 4237 G > A, 4496A > G and 4510G > A SNPs of the *IL12B* gene did not

contribute to the development of AD.[106]

IL12RB1 maps on chromosome 19p13.1. It covers 39.94 kb on the reverse strand. Among eight SNPs (-111A > T, -2C > T, 4443C > T, 5970 G > C, 17183T > C, 17369C > T, 25748T > C and 27637A > T), the TT genotype of the -111A > T SNP (OR = 2.39, 95% CI = 1.41–4.04) and the TT genotype of the -2C > T SNP (OR = 2.55, 95% CI = 1.43–4.57) were significantly associated with an increased risk of AD in a Japanese population.[112]

IL13 maps on chromosome 5q31. It covers 4.85 k on the direct strand. No association between the -1111C > T SNP of *IL13* and AD was found in a Chinese population.[106] The statistically significant association between the -1024C > T SNP of the *IL13* gene and AD was confirmed.[113] In the Japanese population there was no significant association between two SNPs of 704A > C and 1103C > T while the Arg allele of Arg144Gln SNP was significantly associated with an increased risk of AD.[114] A significant association was noted for the A allele of the Arg144Gln SNP and AD (OR = 1.77, 95% CI = 1.06–2.96).[115] In Caucasians, haplotypes consisting of *IL13* Arg144Gln with AD (*P* = 0.006) were associated with AD.[105] None of the three SNPs (-1111C > T, 1293C > T, and Arg144Gln) were associated with AD during the first year.[102]

IL18 maps on chromosome 11q22.2–q22.3. It covers 21.61 kb on the reverse strand. Among five SNPs (-132A > G, -133C > G, -137G > C, -113T > G and 127C > T), the C allele of the -137G > C SNP was associated with an increased risk of AD (OR = 4.28, 95% CI = 1.24–14.77).[116]

TGFB1 maps on chromosome 19q13.2. It covers 52.34 kb on the reverse strand. The C allele (a low TGFβ1 producer allele) of the TGFβ1 915 G > C SNP was associated with an increased risk of AD (OR = 4.8, 95% CI = 2.4–9.7) while there was no statistical significant difference in the frequencies of the 869T > C genotypes.[117] No association between AD and the -590C > T SNP was observed.[102]

TNFα and TNFβ share a common receptor on tumor cells whose expression is upregulated by gamma-interferon.[118] *TNF* maps on chromosome 6p21.3. No significant association was found between -308 G > A SNP of the *TNFα* gene and AD.[103] Neither -1031T > C, -863C > A, -857C > T, -308G > A nor -238G > A SNPs of the *TNFα* gene was associated with AD in a Chinese population.[106] No association was found between AD and -238G > A and -308G > A SNPs of the *TNFβ* gene in a German population.[100] Also, the two SNPs were not linked to AD risk in Americans.[102]

GM-CSF maps on chromosome 5q31.1. It covers 2.38 kb on the direct strand. The A allele of the -677A > C SNP in the promoter region of the *GM-CSF* gene was associated with an increased risk of AD in the United Kingdom (OR = 2.3, 95% CI = 1.4–3.6).[103] Although -1916T > C SNP was significantly associated

with an increased risk of AD (OR = 1.9, 95% CI = 1.2–3.1), there was a strong linkage disequilibrium existed between the -677A > C and -1916T > C SNPs.[103] The 3606T > C and 3928C > T SNPs of the *GM-CSF* gene was not associated with susceptibility to AD in Japanese.[119] There was strong linkage disequilibrium between the two polymorphisms.

STAT6 maps on chromosome 12q13. It covers 16.79 kb on the reverse strand. There was no association between AD risk and the 2964 G > A SNP of the *STAT6* gene while the 13/15-GT repeat allele heterozygosity of the dinucleotide repeat in exon 1 (13-, 14-, 15- and 16-GT repeat alleles) was significantly associated with allergic disease including AD in Japanese.[120] However, the short tandem repeat in exon 1 was not associated with AD risk.[106]

IFNγ maps on chromosome 12q14. It covers 16.25 kb on the reverse strand. In a Chinese population, there was no association between short tandem repeats at the first intron of *IFNγ* gene and AD.[106]

ANTIGEN PRESENTATION MOLECULES

The human major histocompatibility complex (MHC, also called the human leukocyte antigen (HLA) complex) class I molecules are expressed on all human cells except erythrocytes and trophoblasts. HLA molecules are peptide-binding proteins on the surfaces of antigen-presenting cells. The complex of an HLA molecule and bound antigenic peptide forms a specific target for T cell recognition. HLA-A and HLA-B belong to the HLA class I heavy chain paralogues. This class I molecule is a heterodimer consisting of a heavy chain and a light chain. The heavy chain is anchored in the membrane. Class I molecules play a central role in the immune system by presenting peptides derived from the endoplasmic reticulum lumen. The class I molecules generally present antigens to CD8+ T cells, and class II molecules present antigens to CD4+ T cells. They are expressed in nearly all cells. On the other hand, HLA-DM belongs to the HLA class II beta chain paralogues. This class II molecule is a heterodimer consisting of an alpha (DMA) and a beta (DMB) chain, both anchored in the membrane. It is located in intracellular vesicles. HLA-DM plays a central role in the peptide loading of HLA class II molecules by helping to release the class II-associated invariant chain peptide molecule from the peptide binding site. Class II molecules are expressed in antigen presenting cells such as B lymphocytes, dendritic cells and macrophages. Both HLA class I and class II antigens contribute to the pathogenesis of AD.[121] In antigen presentation to cytotoxic T cells with HLA class I molecules, the antigen-processing pathway is controlled by the products of genes that are mapped within the HLA class I region, including low-molecular-weight polypeptide (LMP) and transporters associated with transporter for antigen presentation (TAP). TAP delivers cytosol-derived

peptides into the endoplasmic reticulum, where they bind to nascent HLA class I molecules. TAP is composed of two subunits, TAP1 and TAP2; deficiency of either subunit inhibits TAP function, reducing the supply and repertoire of peptides available for binding to HLA class I molecules. Many diseases associated with HLA have been investigated for the influence of TAP.[122-127] LMP products also have an important role in antigen presentation by class I HLA molecules. LMP subunit 2 (LMP2) and LMP7 are proteasome components, which enhance the proteolytic production of certain peptides.[128,129]

The *HLA* group of genes resides on chromosome 6p21.3. Eleven HLA-A (1, 2, 3, 11, 24, 26, 29, 30, 31, 33 and 66) and 27 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 and 75) alleles are frequently observed in Koreans. Among these, only the A24 allele of HLA was significantly associated with AD.[130] No HLA-DMA (Val140Ile, Gly155Ala, Ile179Thr, 184Arg-His-Cys) and HLA-DMB (144Ala-Glu-Val) alleles were associated with an increased risk of AD.[131]

LMP2 (*PSMB9*) and *LMP7* (*PSMB8*) map on chromosome 6p21.3. *LMP2* and *LMP7* genes encode two subunits of the proteasome, a cytoplasmic catalytic complex involved in the generation of antigenic peptides that are loaded on class I molecules within the endoplasmic reticulum.[132] LMP2/7 subunits may directly affect peptide cleavage specificity.[128,129] One dimorphic site within *LMP2*, Arg60His, and three dimorphic sites within *LMP7*, 3911 G > T, 3912C > T, 4069C > T, have been identified. SNPs of *LMP2* and *LMP7* genes were not significantly different for AD patients and controls.[130]

TAP1 and *TAP2* map on chromosome 6p21.3. *TAP* genes encode a heterodimer involved in the translocation of intracellular peptides across the endoplasmic reticulum membrane where they bind to class I molecules. Genes encoding the two *TAP* subunits, *TAP1* and *TAP2*, are located within the MHC class II region between the DPB1 and DQB1 loci[133,134] and variations in rat *TAP* genes have been reported to be associated with differences in the spectrum of MHC class I-binding peptides.[135] *TAP1* and *TAP2* genes are located at 6p21.3. Two dimorphic sites within *TAP1*, Val333Ile and Gly637Asp, and four dimorphic sites within TAP2, Ile379Val, Thr565Ala, Ala665Thr and Gln687Stop, have been widely investigated.[134] The 333Val and 637Gly alleles of the *TAP1* gene were significantly associated with an increased risk of AD in Tunisians[136] while allelic frequencies of the *TAP1* gene polymorphisms were similar in AD patients and controls.[130] The 565Ala and 665Thr alleles of the *TAP2* gene may be associated with increased risk of AD in a Korean population.[130]

OTHER MOLECULES

Cytotoxic T-lymphocyte-associated antigen-4 (CTLA4,

also known as CD152) is a member of the Ig gene superfamily along with its homologue, CD28, a B7 binding protein.[137,138] CTLA4 is an inhibitory molecule that downregulates T-cell activation. Thus, ligation of CTLA4 on the T-cell surface initiates a cascade of biochemical events that attenuate an ongoing immune response.[139] Allergic diseases are characterized by a defective peripheral T cell tolerance to allergens, suggestive of possible CTLA4 dysfunction.[140,141]

Kallikrein (KLK, stratum corneum chymotryptic enzyme (SCCE)) localizes to the extracellular space of the stratum corneum and is specific for keratinizing cells undergoing desquamation.[142-145] KLK (SCCE) is secreted as an inactive zymogen that is activated by cleavage of an N-terminal peptide. Physiological activators of zymogens remain unknown but *in vitro* studies indicate that some kallikreins can undergo autoactivation while others may be activated by other kallikreins or endoproteases. Apart from its tissue localization, KLK (SCCE) has several properties and characteristics, including the pH and inhibitor profile of catalytic activity, matching the basic prerequisites for a crucial involvement in desquamation under *in vivo* conditions.[143,146,147] Transgenic mice overexpressing human KLK (SCCE) develop changes in their skin similar to those seen in chronic atopic dermatitis.[148] The overexpression of KLK (SCCE) initially may lead to a premature breakdown of the epidermal barrier. This would allow the penetration of irritants and allergens, triggering an inflammatory response, and subsequently a reactive hyperplasia. Therefore KLK (SCCE) is considered to be important in the pathogenesis of AD.

SLC9AR1 (solute carrier family 9, isoform 3 regulatory factor 1) is found in keratinocytes within the granular layer of the epidermis in normal skin and in T-cells and has been implicated in diverse aspects of epithelial membrane biology and immune synapse formation in cells. The downregulation of SLC9A3R1 after T-cell activation is consistent with its role as a negative regulator. SLC9A3R1 could have a similar role in the normal epidermis by modulating the keratinocyte response to a similar immune signal. NAT9 is also found in keratinocytes and T-cells and may play a role in glycosylation. Loss of RUNX1 binding has been shown to be associated with susceptibility to autoimmune diseases such as systemic lupus erythematosus.[149] RUNX1 is involved in CD4 silencing.[150] CD4 repression attributed to a RUNX1 mutation was found in only 18–30% of mature CD8+ T lymphocytes.[150] SNPs lying between *SLC9A3R1* and *NAT9* result in the loss of a RUNX 1 binding site.[151] The loss of RUNX1 sites in alleles associated with autoimmune diseases suggest an important role for RUNX1 in tolerance. It may also suggest defective regulation of SLC9A3R1 or NAT9 by RUNX1 as a susceptibility factor for AD.

Serine protease inhibitor, Kazal-type, 5 (SPINK5) is

thought to be cleaved by furin to yield at least 14 independently working serine protease inhibitory domains.[152,153] Since SPINK5 and many tissue KLKs colocalize in the skin (in lamellar bodies of the uppermost epidermis and the pilosebaceous units of normal human skin tissue),[154] it has been hypothesized that these proteins may be part of a proteolytic enzyme-inhibitor system that controls skin desquamation and shedding.[152,154]

CTLA4 maps on chromosome 2q33. It covers 5.55 kb on the direct strand. CTLA4 is linked to an increased incidence of autoimmune diseases.[155] A SNP at position 49 in exon 1 (49A > G) of CTLA4 exerts differential functional effects on CTLA4 driven down-regulation of T-cell activation.[156-158] The 49A > G SNP leads to a threonine to alanine change in the lead peptide. The 49A > G SNP of CTLA4 gene was not correlated with AD, however.[159]

KLK7 gene maps on chromosome 19q13.33. It covers 7.57 kb on the reverse strand. Among all serine proteases within the human genome, the tissue KLK (SCCE) cluster is the largest. This cluster includes fifteen genes tandemly located on chromosome 19q13.4. KLKs generally share 30–50% sequence identity at the nucleotide and amino-acid levels.[160] The KLK5 and KLK7 genes were originally identified from a keratinocyte library and their products were first named human stratum corneum tryptic enzyme (hK5)[161] and human stratum corneum chymotryptic enzyme (hK7).[162] These KLKs seem to catalyze the degradation of intercellular structures in the most cornified layer of the skin and contribute to the normal cell shedding process at the skin surface.[163,164] KLK5 and KLK7 have been implicated in skin and brain diseases.[160,165,166] Recent studies have also revealed alterations of their expression in hormone-dependent cancers.[167-169] A 4-bp insertion was identified in the 3' untranslated region of the KLK7 (SCCE) gene. The common allele was AACC, and the rare allele was AACCAACC. A significant genetic association was found between the rare AACCAACC variant of the KLK7 (SCCE) gene and AD.[170]

Both SLC9A3R1 and NAT9 map on chromosome 17q25.1. The RUNX1 gene maps on chromosome 21q22.3. A SNP is located between the SLC9A3R1 and NAT9 genes in chromosome segment 17q25. This SNP occurs within a consensus binding site motif for RUNX1, a factor required for both differentiation and proliferation of haematopoietic cells. There was no significant allelic association between the RUNX1 polymorphism (rs734232) and AD in a small Japanese adult population.[171]

The serine protease inhibitor Kazal type 5 gene (SPINK5) expresses the 15 domain serine protease inhibitor lymphoepithelial Kazal-type-related inhibitor, named LEKTI.[172] SPINK5 is located on chromosome 5q32 within a genomic region that has previously been linked to AD by a genome-wide linkage

study and, consequently, SPINK5 has been implicated as a putative susceptibility gene for common, nonsyndromic AD.[173] Subsequently, Walley et al. reported a significant association of a nonsynonymous SNP located in exon 14 of SPINK5, consisting of a G-to-A transition (1258G > A) that leads to a Glu420Lys substitution in the encoded protein. In individuals affected by AD, a significant maternal over-transmission of the risk allele to their children was demonstrated.[173] Fölster-Holst et al.[174] studied 8 SNPs in different regions of the SPINK5 gene, including 4 nonsynonymous SNPs leading to an amino acid change (Asp106Asn, Asn368Ser (1103A > G) and Asp386Asn (1156G > A), and Glu420Lys (1258G > A), Gly463Gly, Val553Val, Leu756Leu and Gly804Gly). None of the SNPs were associated with an increased risk of AD. Kato et al. examined associations between 8 SNPs (IV12-26C > T, IVS12-10A > G, IVS14 + 19 G > A, IVS 13-50 G > A, 1103A > G, 1156 G > A, 1188T > C, 1258G > A) of the SPINK5 gene and AD in a Japanese population and found a positive association of 7 SPINK5 SNPs (except for 1156G > A) with AD.[175] Nishio et al.[176] also reported a significant association between SPINK5 1258G > A and AD risk. No statistically significant association between SPINK5 1258G > A genotypes and AD was observed in a large German population.[177]

DRUG-METABOLIZING ENZYMES

The picture of drug-metabolizing enzymes is complicated, because AD is polygenic in nature, and susceptibility is also influenced markedly by environmental factors. In addition, evidence is emerging that certain metabolic polymorphisms may influence the pathogenesis of allergy. The metabolism of xenobiotics includes oxidation, reduction, and hydrolysis (phase I) and conjugation (phase II) reactions.[178,179] Glutathione S-transferase (GST) enzymes belong to the phase II detoxification system and are responsible for biotransformation and degradation of certain electrophilic compounds. Oxidative stress, with the formation of reactive oxygen species (ROS), is a key component of inflammation.[180] Members of the GST supergene family are critical for protecting cells from ROS because they can utilize a wide variety of products of oxidative stress as substrates and also influence the synthesis of eicosanoid-like mediators via modulation of ROS levels.[181,182]

N-acetyltransferase (NAT) is one of the conjugation enzymes and transfers acetate from acetyl coenzyme A to the functional groups of primary arylamine and hydrazine to form acetamides and hydrazides, in xenobiotics, containing arylamine and hydrazine groups[178,179,183] NAT enzymes, NAT1 and NAT2, are involved in the metabolism of these carcinogens via O- and N- acetylation.[184] Therefore, NAT2 and NAT1 are involved in the detoxification and bioactivation of carcinogens.[185,186] Individuals in a population are