Molecular Genetic of Atopic dermatitis: An Update

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Abstract

Atopic dermatitis (AD) is a chronic multifactorial inflammatory skin disease. The pathogenesis of AD remains unclear, but the disease results from dysfunctions of skin barrier and immune response, where both genetic and environmental factors play a key role. Recent studies demonstrate the substantial evidences that show a strong genetic association with AD. As for example, AD patients have a positive family history and have a concordance rate in twins. Moreover, several candidate genes have now been suspected that play a central role in the genetic background of AD. In last decade advanced procedures similar to genome-wide association (GWA) and single nucleotide polymorphism (SNP) have been applied on different population and now it has been clarified that AD is significantly associated with genes of innate/adaptive immune systems, human leukocyte antigens (HLA), cytokines, chemokines, drug-metabolizing genes or various other genes. In this review, we will highlight the recent advancements in the molecular genetics of AD, especially on possible functional relevance of genetic variants discovered to date.

Keywords: Atopic dermatitis, molecular genetics, immune genes, cytokine, chemokine, drug-metabolizing genes.

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Introduction

Atopic dermatitis (AD) is a very frequent multifactorial chronic inflammatory skin disorder and is characterized by xerosis, pruritus and erythematous lesions with increased transepidermal water loss. [1] Despite the power of molecular approaches and persistent investigative efforts, AD remains an enigmatic disorder and the agent (or agents) triggering this skin disorder remains to be completely identified. AD is thought to be associated with the dysfunctioning of skin barrier and Th2 cell adaptive immune responses to common environmental allergens. It is a disease with complex genetic and environmental susceptibility factors. Although it is likely that many genetic loci are involved, the association of filaggrin (FLG) null mutations with AD has provided a major step forward in our understanding of disease pathogenesis. [2] FLG is expressed in keratinocytes and is thought to have a role in skin barrier function, cutaneous pH, and hydration. [3] Several clinical phenotypes of AD have now been discovered, but they exhibit great variations in disease severity among affected individuals. [4] Moreover, some cases have the atopic march, while others are susceptible to skin infections such as staphylococcus aureus, eczema herpeticum and malassezia. [4] Approximately 80% of AD patients have raised serum of immunoglobulin E (IgE) and/or immediate skin test reactivity to allergens. [5-7] Advances in genomic medicine have improved our understanding of the human genome's contribution to health and disease. Genome wide association studies (GWAS) are proved to be a powerful method for identifying disease susceptibility genes for common human diseases and has begun to reveal underlying cellular pathways and point to new therapeutic approaches. [8] This review focuses on the recent advancement of the molecular genetics of atopic dermatitis, especially on the genes located within and around the susceptible loci and their possible roles in pathogenesis of atopic dermatitis. Before beginning of discussion on the molecular genetics, we will highlight the factors that influence on the skin barrier abnormalities.

Factors influence on skin barrier dysfunctions

It has now been well established that FLG derived natural moisturizing factors (NMFs) are important in maintenance of epidermal water and low acidity thus preserving the barrier function of outermost stratum corneum. [9] FLG is involved in the development of keratinocytes to maintain epidermal integrity and it is an important marker of keratinocytes differentiation. During keratinocytes differentiation, profilaggrin is dephosphorylated and degraded into 10-12 FLG molecules, which condense in the cytoskeleton of keratin to form an intensive protein-lipid matrix. Consequently, these FLG monomers are degraded into NMFs, which are important to maintain skin water, a low pH or maintaining the barrier function of the stratum corneum (Fig. 1).

Recently, it has been reported that intragenic copy number variation (20–24 copies in one person) within a FLG gene contributes to the risk of AD with a dose-dependent effect. [10] Profilaggrin may prevent the extracellular secretion of lamellar bodies, as contain lipids, and may block or decrease the degradation of FLG, which results in reduce in the production of NMFs. Reduced production of acidic metabolites of FLG results an increase of skin surface pH or activating neutral pH dependent kallikreins with downstream influences on skin barrier function. [11, 12] An increased pH may also decrease the β-glucocerebrosidase activity and sharing lipid-processing defect may delay epidermal barrier recovery. [11-13] Also, the elevated pH takes place a decrease in acidic sphingomyelinase catalytic activity and causes degradation of β-glucocerebrosidase and acidic sphingomyelinase. [11-13] These enzymes playing main role in ceramide synthesis. Ceramides are essential lipid moieties that are included in preserving epidermal permeability barriers. Thereby, a change in epidermal surface pH may regulate homeostasis of the epidermal permeability barrier, as well as stratum corneum integrity and cohesion. The following are the factors influence on FLG expression in AD. (A) Loss-of-function mutations of FLG result in decreased or totally absent levels of FLG. [14-16] The prevalence of FLG mutation in Northern European subjects about 10% whereas in Chinese, Japanese, and Korean subjects range from 3% to 6%, [16]however, in certain

Northern European populations with AD, the prevalence of FLG mutations is reach to 25%: 50%. [2] Consistently focusing in the research of AD for more than 20 year on genetic factors, recent strong role of a genetically predetermined skin barrier disturbance came to a large extent from the discovery the linkage

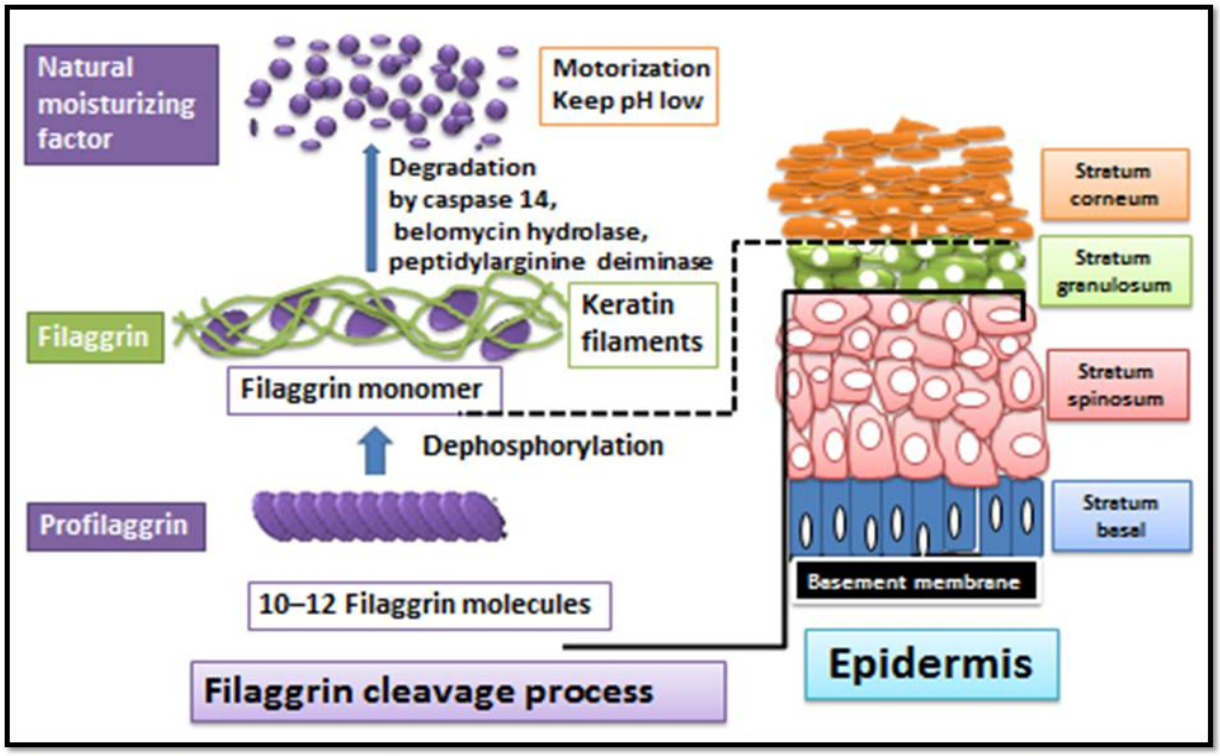

Figure 1. Cleavage of profilaggrin into natural moisturizing factors via degradation of filagrgrin molecules. Filagrgrin is involved in the development of keratinocytes to maintain epidermal integrity and it is an important marker of keratinocytes differentiation. (after Kabashima, 2013 [9]).

between the development of AD and loss-of-function mutations in the gene encoding FLG. [14-16] (B) Expression of epidermal FLG is down regulated by cytokines IL-4, IL-13, IL-17A, IL-22, IL-25, IL-31, TNF-α in AD patients. [17-23] (C) Effect of environmental factors which lead to FLG proteolysis such as low ambient humidity, skin irritants, pruritus / excoriations / mechanical damage, age and water. [24, 25] Later will be reviewed the genetic variation of FLG.

Study on single nucleotide polymorphism of the claudin-1 gene (CLDN1) in AD patients demonstrated that tight junctions contribute to the barrier dysfunction and immune dysregulation in AD patients and this may be mediated in part by reductions in tight junction protein claudin-1. [26] In addition, it is also reported that activation of toll like receptor (TLR)-2 plays a role on tight junction barrier via the protein kinase in the tight junction biogenesis. [27] Moreover, IL-4 and IL-13 also promote keratinocyte CLDN-1 expression. [27] Thus TLR-2 activation enhanced expression of CLDN-1 in keratinocytes of AD patients. In addition, TLR-2 lacking mice showed delayed or incomplete barrier recovery. [28] These genetic modifications of TLR-2 might lead to barrier dysfunctions and predispose in AD patients.

Evidences of the genetics role in atopic dermatitis

Recent advancements in clinical experience and molecular reseach on atopic dermatitis have strongly been influenced by genetically alterations. [29] All identified major candidate genes for AD pathogenesis has been listed in Figure 2. Studies on twin have provided the role of a genetic background with a concordance rate of 72–86 % in identical

twins and 21–23 % in dizygotic twins, indicating high heritability of AD. [30, 31] In addition multiple studies on affected individuals and their families have a positive family history of AD. However the heritability of AD was determined at 72 % by study on Norwegian twin. [31] Recently, a total of 19 susceptibility loci have been estimated at a genome-wide level of significance. Contribution of such these genetic factors may affect diverse phenotypes of AD among individuals. Hence the disease seems to be caused by genetic factor that lead to an immune system deregulation. However deficiencies in innate and adaptive immunity based on, endogenous factor as genetic predisposition result in skin barrier dysfunction and exogenous factor as hyper reactivity to environmental stimuli and susceptibility to skin infections which influence the course and severity of AD. In fact the pathogenesis of AD has been attributed to a complex and multifactorial interactions of the environment and host susceptibility genes, altered skin barrier function, the immune system, and pruritus. [6]

Molecular genetic tools of atopic dermatitis

In progress of biotechnology and molecular biology, more candidate genes have now been determined to be associated with AD. According to the available knowledge, the genes that are related to the structural abnormalities of the epidermis and immune dysregulation play a pivotal role in the etiology of AD. [32] Human genetic variants are either common or rare, common variants, known as polymorphisms and are defined as variants with a minor allele frequency of at least 1% within the population. [30, 31] Single nucleotide polymorphisms (SNP) are the most common uses for determining of genetic variations within individuals. [33] Recently GWAS comprehensively surveys associations between SNP in common diseases. [34] Genome-wide linkage analysis had been used in different populations to date, and multiple candidate regions on multiple chromosomes had been associated with AD. [35-39] The linkage regions vary in different populations, and there is no extensive overlap among studies. Some candidate regions are close to functional genes linked to the various phenotypes of AD. Systemic, well-powered, genome-wide surveys using GWAS and immunochip analyses have estimated the relationship between SNP and susceptibility to AD. [31, 39, 40] It is well established that common loss of function variants of FLG are a major predisposing factor for AD. As for example, the FLG mutations are involved in AD and are featured in some review articles. [31, 42-45] The AD associated major candidate genes and their chromosomal location or genetic variations have been summarized in Table 1. The following genes play a central role in the pathogenesis of AD and now have been offered a several novel potential therapeutic opportunities for AD.

Table 1: Atopic dermatitis associated candidate genes and their chromosomal location and genetic variation in different population.

Gene Symbol	Gene name	Chromosomal location	Genetic variation	Population	References
FLG	Filaggrin	1q21	R501X-2282del4	Caucasian Northern-American European and Asian ancestry, Chinese German	(Palmer et al. 2006) (Brown and McLean 2012; Hu et al. 2009; Brown et al. 2008;Ekelund et al. 2008; Barker et al. 2007; Morar et al. 2007; Weidinger et al. 2005)
			S2377X (FLG2)	Irish	(Ekelund et al. 2008)
			Q294X (TCHHL1)		(Marenholz et al. 2006)
			R501X, 2282del4,	Japanese	(Brown and McLean 2012)
			E2554X, R2447X,	African	(Osawa et al. 2010)

			1249insG, R826X, 2767insT, E2422X P478S	Americans Chinese	(Margolis et al. 2014; Winge et al. 2011) (Polcari et al. 2014) (Kim et al. 2009)
SPINK5 (LEKTI)	Serine Protease Inhibitor Kazal-Type 5 and Lymphoepithelial Kazal-Type-Related Inhibitor	5q31	1258G > A IV12-26C > T IVS12-10A > G IVS14 + 19 G > A IVS 13-50 G > A 1103A > G 1156 G > A 1188T > C 1258G > A	Japanese	(Kato et al. 2003; Nishio et al. 2003)
MHC (HLA)	The major histocompatibility complex or human leukocyte antigen	6p21	A24 allele of HLA **TAP1**, Val333Ile Gly637Asp **TAP2**, Ile379Val Thr565Ala Ala665Thr Gln687Stop	Korean Tunisians Korean	(Lee et al. 2001) (Ismail et al. 1997) (Braff et al. 2005)
Innate Immune genes					
CARD4 (NOD1)	Caspase recruitment domain-containing protein 4	7p15-p14	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)	German	(Weidinger et al. 2005)
CARD15 (NOD2)	Caspase recruitment domain-containing protein 15	16q21	2104C > T 2722 G > C 802T > C 534 G > C rs1077861 (intron 10A > T) 2863 G > A 4278A > G 60A > G	German	(Weidinger et al. 2005; Kabesch et al. 2003)
CD14	Monocyte differentiation antigen	5q22-q32	159C > T 1145 G > A, 1359 G > T and -550C > T	Chinese German Singaporean Chinese	(Lange et al. 2005) (Sengler et al. 2003) (Liang et al. 2006)
(MBL2)	Mannose-binding lectin	10q11.2-q21	Gly54 Asp	Japanese	(Hashimoto et al. 2005)

TLR2	Toll-like receptor 2	4q32	R753Q A-16934T 2258G/A, 896A/G (rs4696480 (T > A), rs3804099 (T > C), rs3804100 (T > C), rs5713708 (G > A)	German Italian Italian Ukrainian German	(Niebuhr et al. 2010; Mrabet-Dahbi et al. 2008; Niebuhr et al. 2008) (Salpietro et al. 2011) (Salpietro et al. 2011) (Levchenko et al. 2013) (Potaczek et al. 2011; Oh et al. 2009)
TLR4	Toll-like receptor 4	9q32-q33	rs4986790 (A > G) rs4986791 (C > T) (rs2770150 (T > C), rs6478317 (A > G), rs1927911 (C > T), rs2149356 (C > T), rs4986790 (A > G), rs4986791 (C > T), rs7873784 (G > C), rs1927906 (A > G) A-896G	Italian Ukrainian German German	(Salpietro et al. 2011) (Levchenko et al. 2013) (Oh et al. 2009; Weidinger et al. 2006) (Weidinger et al. 2006)
TLR6	Toll-like receptor 6	4p14	Ser249Pro rs5743810 (T> C) T597C C1350T	German Dutch	(Hoffjan et al. 2005)
TLR9	Toll-like receptor 9	3p21.3	C-1237T	German	(Novak et al. 2007)
DEFB1	Human β-defensin 1	8p23	2266T>C 1241T>G 692 A>G 1654 A>G 20 G>A 5'-UTR 44 C>G 5'-UTR 52 G>A 5'-UTR	Korean Egyptian Mexican Brazilian	(Kim et al. 2009) (Mohamed et al. 2009) (Prado-Montes et al. 2007) (Segat et al. 2010)
Cytokines and related genes					
IL-4	Interleukin 4	5q31–33	−590 C/T 1098G/T *589C>T* −33 C/T	Egyptian Czech Japanese Chinese Czech Macedonian Candian Egyptian	(Hussein et al. 2014) (Kayserova et al. 2012) (Walley et al. 2001) (Chang et al. 2006) (Kayserova et al. 2012) (Stavric et al. 2012) (He et al. 2003) (Hussein et al. 2014)
IL-4R α	Interleukin 4 receptor alpha	16p11.2-12.1	-3112C > T, -1803T > C, -327C > A, -326A > C -186G > A 1727G > A 1199C > A, 1242T > G,	Japanese British, Japanese Chinese	(Hosomi et al. 2004) (Callard et al. 2002) (Chang et al. 2006; Oiso et al. 2000)

			1507C > T 1727G > A I50 V Q576R 3223C/T	Egyptian Japanese	(Hussein et al. 2014) (Hosomi et al. 2004)
STAT6	signal transducer and activator of transcription	12q13.3–q14.1	2964 G > A 2892 C/T 1315-GT repeat in exon 1	Egyptian Chinese Japanese	(Hussein et al. 2014) (Chang et al. 2006) (Tamura et al. 2003)
IL-10	Interleukin 10	1q31-q32	1082A > G 819T > C 592A > C 1082A/G, -819C/T, -592A/C --7616AGG	Macedonian Chinese German Czech	(Stavric et al. 2012) (Chang et al. 2006) (Hosomi et al. 2004) (Kayserova et al. 2012)
IL-6	Interleukin 6	7p21	-174C > G -922A > G -174C/G nt565A/G	German Czech	(Hosomi et al. 2004) (Kayserova et al. 2012)
TNF-α	Tumor necrosis factor alpha	6p21.3	-308 G > A 1031T > C, -863C > A, -857C > T, -308G > A -238G > A AG cdn25	British Chinese Macedonians	(Rafatpanah et al. 2003) (Chang et al. 2006) (Stavric et al. 2012)
TNF-β	Tumor necrosis factor beta	6p21.3	238G > A 308G > A	German	(Hosomi et al. 2004)
IL-1 α	Interleukin 1 alpha	2q14	-899T > C	Macedonians	(Stavric et al. 2012)
IFNγ	Interferon gamma	12q14	874 A>T	Macedonians	(Stavric et al. 2012)
IL-1β	Interleukin 1 beta	2q14	511C > T, 3953T > C, 3953T > C 1418T > C 315T > C	German British Macedonian	(Hosomi et al. 2004) (Rafatpanah et al. 2003) (Stavric et al. 2012)
IL1RN	Interleukin 1 receptor antagonist	2q14.2	variable number of tandem repeat in intron 2	German	(Hosomi et al. 2004)
IL1RL1 (ST2)	Interleukin 1 receptor-like 1 (Suppression of tumorigenicity 2)	2q12	26999G > A 2992C > T, 5283G > A, 5860C > A, 11147C > T, 744C > A 27639A > G	Japanese	(Shimizu et al. 2005)
IL-5	Interleukin	5q31.1	703C > T	Japanese	(Yamamoto et al. 2003)

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IL-12β	Interleukin 12beta	5q31.1-q33.1	1188A > C 4237 G > A, 4496A > G 4510G > A	Japanese Chinese	(Tsunemi et al. 2002) (Chang et al. 2006)
IL-12Rβ	Interleukin 12 receptor beta	19p13.1	111A > T 2C > T, 4443C > T 5970 G > C 17183T > C 17369C > T 25748T > C 27637A > T	Japanese	(Takahashi et al. 2005)
IL-13	Interleukin 13	5q31	1111C > T 1024C > T 704A > C 1103C > T Arg144Gln Arg 130 Gln 1111C > T, 1293C > T, Arg144Gln	Chinese Japanese German Japanese German Canadian German Japanese	(Chang et al 2006) (Tsunemi et al. 2002) (Hummelshoj et al. 2003) (Tsunemi et al. 2004) (Folster-Holst et al. 2005) (He et al. 2003) (Hummelshoj et al. 2003) (Tsunemi et al. 2002)
IL-18	Interleukin 18	11q22.2-q22.3	132A > G, 133C > G 137G > C, 113T > G 127C > T	German	(Novak et al. 2005)
TGF β1	Transforming growth factor beta 1	19q13.2	1 915 G > C 869T > C 590C > T	British	(Arkwright et al. 2001)
GM-CSF	Granulocyte macrophage colony-stimulating factor	5q31.1	677A > C 1916T > C 3606T > C 3928C > T	British Japanese Canadian	(Rafatpanah et al. 2003) (Saeki et al. 2006) (He et al. 2003)
IL-9	Interleukin 9	5q31–35	4091G>A	Korean	(Namkung et al. 2011)
IL-9R	Interleukin 9 receptor	Xq/Yq	1737C>T	Korean	(Namkung et al. 2011)
Chemokines and related genes					
CCL5 (RANTES)	Chemokine (C-Cmotif) ligand 5 (Regulated upon activation, normally T	17q11.2- q12	28C>G 403 G>A 2518A > G	German Japanese Hungarian	(Nickel et al. 2000) (Bai et al. 2005) (Kozma et al. 2002)

	cell expressed +secreted)				
CCL11	chemokine(C-Cmotif) ligand 11 (eotaxin 1)	17q21.1- q21.2 2	426C > T, 384A > G	Japanese	(Wakugawa et al. 2002)
CCL17 (TARC)	chemokine(C-Cmotif) ligand 17 (Thymus and activation-regulated chemokine)	16q13	431C > T	Japanese	(Gangur and Oppenheim 2000)
CCR3	Chemokine (C-Cmotif) receptor3	3p21.3	1052T > C	American	(Tsunemi et al. 2003)
CCR4	Chemokine (C-Cmotif) receptor 4	3p24	1014C > T	Japanese	(Tsunemi et al. 2004)
CMA1	Mast cell chymase 1	14q11.2	(-1903A > G	Japanese Italian	(Iwanaga et al. 2004) (Weidinger et al. 2005)
Drug-metabolizing genes					
GSTP1	Glutathione S-transferase pi	11q13	1404A > G 2294C > T	Russian	(Safronova et al. 2003)
NAT	N-acetyl transferase	8p23.1-p21.3	481C > T 590G > A 857G > A	Russian Caucasian	(Makarova et al. 2005) (Ueda et al. 2003)
Other genes					
CTLA4 (CD152)	Cytotoxic T-lymphocyte-associated antigen-4	2q33	49A > G	Chinese	(Yang et al. 2004)
KLK (SCCE)	Kallikrein (stratum corneum chymotryptic enzyme)	19q13.33	AACCAACC variant of the KLK7 (SCCE)	British	(Vasilopoulos et al. 2004)
RUNX1	Runt-related transcription factor1 binding site between solute carrier		rs734232	Japanese	(Hosomi et al. 2004)
IRF-2	Interferon regulatory factor 2	4q35	829C>T 830C>T 684C>T 467G>A 921G>A),	Japanese	(Nishio et al. 2001)

			10-bp deletion in 3' UTR 1739[ATCCC]8>6		
FCER1B	High affinity IgE receptor beta chain	11q13	RsaIin2, RsaIex7	British	(Cox et al. 1998)
PHF11	Plant homeodomain Zink finger 11 protein	13q14	intron3 T>C 3UTR G>A	Australian	(Jang et al. 2005)

1- Filaggrin Gene

FLG gene is located on chromosome 1q21 in a region called the epidermal differentiation complex. It is one of genes that code for S100-fused-like proteins (SFTP) which harbor several proteins e.g. profilaggrin (FLG), hornerin (HRNR), FLG-2 (FLG2), repetin (RPTN), cornulin (CRNN), trichohyalin (TCHH), and trichohyalin-like 1(TCHHL1). [41] These genes are very similar together in structure and function, and locate in close proximity to each other in the epidermal differentiation complex. [13,41,42] On the basis of previous illustrations with FLG, it has been postulated that a stop-gain (null) mutation in exon 3 of any of the SFTP genes may be result in reduced or absent protein production. [41-44] Genetic associations of FLG mutations with AD were confirmed and further verified by many independent groups using numerous cohorts of different populations e.g. American, [45] Caucasian and Northern-American AD, [2] European and Asian ancestry, [43,46-51] Chinese, [52] German, [53] Irish, [43] and Japanese. [54] More than 40 FLG loss-of-function mutations have been described in Europeans and Asians. [43] While in African-American children with AD revealed a total of 289 variants in FLG, 107 variants in FLG2, 339 variants in HRNR, 4 variants in RPTN, 37 variants in CRNN, 88 variants in TCHH, and 14 variants in TCHHL1. In addition three novel identified FLG stop-gain mutations, Q570X, R3409X and S3707X, were investigated only once. S2392X and S2377X in FLG2 were indicated 1 and 16 times, respectively. However, none of these variants could be detected in other members of African-American PEER children cohort. In TCHHL1, the variant Q294X was noted twice. [43-45, 55, 56] These findings are in agreement with those of Winge et al., who also failed to detect common FLG loss-of-function mutations in people of African ancestry with AD. [55] Their report is from the largest whole-exome sequencing study of African Americans with AD suggesting that S2377X (FLG2) and Q294X (TCHHL1) variants may not be clinically important with respect to incident AD and it seems unlikely that FLG stop-gain mutations have a prominent role with respect to incident AD in African Americans children. [55,56] Whereas, the recent demonstration that FLG2 mutations increase the persistence of AD in African Americans [57] further suggests a pathogenic role for FLG2 mutations (rs12568784 and rs16833974) and supports the sequencing of FLG2in African Americans with IV with or without AD. [44] Polcari data was demonstrated a prevalence of filaggrin mutations including R501X, 2282del4, E2554X, R2447X, 1249insG, R826X, 2767insT, and E2422X in the African American population that exceeds previously published data, although the overall prevalence is still lower than in other populations. [58] In addition other study was added that the FLG P478S polymorphism alone and combined with other factors influences free fatty acids levels and increases the susceptibility to AD among Chinese population. [59]

2- SPINK5 and LEKTI gene

The Serine Protease Inhibitor Kazal-Type 5 (SPINK5) gene located on chromosome 5q32 within genomic region has been linked to AD and encodes a 15-domain protease inhibitor Lymphoepithelial Kazal-Type-Related Inhibitor (LEKTI) which is expressed in epithelial and mucosal surfaces and in the thymus. In fact Serine protease enzymes play an important role in skin barrier homeostasis, including SC desquamation, lipid barrier construction and cornified cell envelope. While, SPINK5 participates to the regulation of proteolysis in keratinocyte differentiation and the generation

of normal epithelium, and LEKTI had been found to be involved in maintaining the permeability of normal skin. SPINK5 polymorphisms are associated with the incidence and severity of AD among Chainese, [60, 61] athough no association was confirmed with AD in German. [62] Otherwise, a recent study was suggested that the E420K LEKTI variant is a risk factor for AD through an increase in the TSLP expression. [63] Subsequently, recent studies found a significant association between (1258G > A) SPINK5 polymorphism and AD in Japanese, [64, 65] and in German. [66] In individuals affected by AD, a significant maternal over-transmission of the risk allele to their children was demonstrated Walley et al. [67] Folster-Holset al., studied 8 SNPs in different regions of the SPINK5 gene, including 4 non-synonymous SNPs leading to an amino acid change (Asp106Asn (G316A), Asn368Ser (1103A > G) and Asp386Asn (1156G > A), and, Gly463Gly (A1389G), Val553Val (C1659T), Leu756Leu (C2358T) and Gly804Gly C2412T) and Glu 825Asp (C2475T)). [62] 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, Asn 368Ser (1103A > G), Asp 386Asn (1156 G > A), His 396His (1188T > C), Glu 420Lys (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. [64, 65] In addition a study of Six SNPs rs17718511, rs17860502, KN0001820, rs60978485, rs17718737, and rs1422985 in the SPINK5 gene provides evidence for a significant interaction between the SPINK5 gene that may contribute to AD susceptibility among Korean. [68]

3- MHC (or HLA) genes

The major histocompatibility complex (MHC) (also known as human leukocyte antigen (HLA) complex) is classified into three classes. Human leukocyte antigen class-I (HLA-I) sub-classified as A, B, and C, are produce by all human cells except erythrocytes and trophoblasts The HLA group of genes located at chromosome 6p21.3. Eleven HLA-A (1, 2, 3, 11, 24, 26, 29, 30, 31, 33 and 66) and twenty seven 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 found in Koreans. Among these, only the twenty four alleles of HLA were significantly associated with AD. [69] The 333 Val and 637 Gly alleles of the transporter for antigen presentation 1 (TAP1) gene were significantly associated with susceptibility to AD among Tunisians population, [70] while allelic frequencies of the TAP1 gene polymorphisms were not associated with the disease. [69] The 565Ala and 665Thr alleles of the TAP2 gene may be associated with susceptibility to AD in a Korean population. [69]

4- Innate Immune system genes

As components of innate immunity, antimicrobial peptides (AMPs) produced by keratinocytes play a crucial role in the clearance of microbial pathogens and in preserving epidermal barrier effectiveness. Consequently deficiencies in these AMPs play roles in the pathogenesis of AD. Mainly AMPs include proteins from the β-defensin family (hBD-1, 2, and 3), cathelicidins, psoriasin, and ribonuclease (RNase). [71] Mutations in PRRs s and AMPs are play roles in the initiation and exacerbation of AD. However pattern-recognition receptors (PRRs) help protect organisms from microbial pathogens such as *Staphylococcus aureus (S. aureus)* and Malassezia furfur (M. furfur). Generally, in AD patients, AMPs expression is not reduced, but significantly varies according to the type of AMPs. [5] Recent progress has revealed that innate immune responses are initiated by pattern-recognition receptors (PRR) 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. [72,73] Mutations in PRRs such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain like receptors (NLRs), as well as mutations in AMPs are associated with susceptibility to skin infections and play key roles in the initiation and aggravation of AD. [74,75] The following are the genes associated innate immune system and have a role in AD pathogenesis.

4 (a) - CARD4 (or NOD1) gene

Caspase recruitment domain – containing protein (CARD) 4 is located at chromosome 7p15-p14 and about 54.49 kb in length. Eleven

CARD4 or nucleotide – binding oligomerization domain protein (NOD)1 polymorphisms, 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 associated with AD. 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. [76]

4 (b) - CARD15 (or NOD2) gene

CARD15 is located at chromosome 16q21 and about 39.45 kb in length. No significant associations between AD and any polymorphisms (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. [77] 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 of developing AD in German. [78]

4 (c) - Monocyte differentiation antigen (or CD14) gene

CD14 gene is located at chromosome 5q22-q32 and about 1.95 kb in length. In a small study, children with the CT genotype of the CD14−159C > T SNP had a significantly lower prevalence of AD at three years of age compared with those with the genotypes CC and TT combined, [79] although the CD14-159C > T SNP was not associated with an increased risk of AD in German children. [80] No significant difference was found in the genotype frequencies of -159C > T, -1145 G > A, 1359 G > T and -550C > T SNPs between AD patients and controls. [81]

4 (d) - MBL2 gene

The mannose-binding lectin **(**MBL2) gene is located at 10q11.2-q21 chromosome and about 6.32 kb in length. 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. [82]

4 (e) - TLR2, TLR4, TLR6 and TLR 9 genes

Toll-like receptor (TLR)-2, TLR4, TLR6 and TLR9 are located at chromosome 4q32, 9q32-q33, 4p14, and 3p21.3, respectively. The TLR2 R753Q polymorphism modulates the innate and adaptive immunity through control of cytokine production (IL-2, IL-6, IL-8, and IL-12), and via changing TLR2 and CD36 expression in AD cases [83-85]. TLR2 rs5743708 (A > G) polymorphisms were demonstrated among Italian, Ukrainian and German children with severe AD, [86, 87] while AD patients exhibit a higher frequency of the TLR4 polymorphisms rs4986790 (A > G) among Italian and among Ukrainian, [86, 87] and rs4986791 (C > T) among German [88, 89]. 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. The TLR4 A-896 G polymorphism was associated with severe AD patients. [90] There was no association between the TLR6 rs5743810 (T> C) polymorphism and risk for AD. While T597C TLR6, C 1350T TLR6 were associated with AD in German and Dutch. [91, 92] Moreover, C-1237T TLR9 promoter polymorphism had been found in AD patients. [93]

4 (f) - DEFB1 gene

The human β-defensin 1 **(**DEFB1) gene is located at 8p23.2266T/C and 1241T/GSNPs of DEFB1 gene had been demonstrated to be associated with AD among Korean. [94] While 692 A>G and 1654 A>GSNPs of DEFB1 gene had been demonstrated to be associated with AD among Egyptian, [107] and among Mexican populations. [95, 96] As controversial findings have been achieved, a study had been not confirmed that the role of -20 G/A (rs11362), -44 C/G (rs1800972), and -52 G/A (rs1799946) at 5'-UTR of DEFB1 gene in the development of AD among Brazilian population. [97]

5- Adaptive immune system genes:

Alterations in the adaptive immune system are also play key role with AD. Where AD is going through a biphases, the first phase is prevailed by T helper type 2 (Th2) cytokines that later turns to the second phase a more chronic Th1-dominated eczematous phase. The effective elevation of IgE in atopic disease by B cells depends on support by Th2 cells, which mainly produce interleukin-4 (IL-4), IL-5, IL-9 and IL-13. Adaptive immune genes are including cytokine genes and chemokine.

5(a) - Cytokines and related genes:

Cytokines have been classified into two subgroups according to their function: 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 humeral machinery. Some cytokines, such as IL-1α, IL-2, and TGF-βwere found to be decreased in AD, [98, 99] while other such as IFN-γ, IL-12 and GM-CSF were elevated in chronic AD. Several data have been shown the association between cytokine polymorphism and AD. Some reports show positive association of certain cytokine polymorphisms with AD, while others are controversial. [100]

5(a-1) - IL-4 gene

Interleukin (IL)-4 is a glycoprotein encoded by the IL-4 gene which has been mapped to chromosome 5q31–33 and about 9.01 kb in length. Promoter polymorphisms of IL-4-590C/T were significantly associated with atopic AD in Egyptian population, [101] Czech population, [102] and Japanese population. [67] On contrast, IL-4-590C/T SNP of IL-4 was not associated with AD in Chinese, [103] Egyptian [101] and Czech population. [102] IL-4 -1098G/T polymorphism was significantly associated with atopic AD in Czech population, [102] while no association in Macedonians. [104] No association was found between AD and -33C/T,IL-4 polymorphism in Chinese, [103] Czech [102] and Macedonians population. [104] In Caucasians the T allele of IL- 4 -589C>T SNP was significantly associated with the development of AD at 24 months of age. [105]

5(a-2) - IL-4Rα gene

Interleukin 4 receptor alpha gene (IL-4Rα) is located at chromosome 16p11.2-12.1 and about 50.86 kb in length. Several IL4R polymorphisms (-3112C > T, -1803T > C, -327C > A, -326A > C and -186G > A) have been found to associated with AD in Japanese. [106] Seven polymorphisms (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 in British. [107] It has been demonstrated that the 1727G > A SNP (Gln551Arg) was significantly associated with AD in another Japanese population. [108] In contrast no association between (1199C > A, 1242T > G, 1507C > T and 1727G > A) of IL4R polymorphism and AD in a Chinese population. [103] Inaddition in Egyptian population the IL-4Rα I50 V and Q576R, polymorphisms were significantly associated with the development of AD. [101] Another polymorphism 3223C/T IL4Rα was associated with AD in Japanese. [106]

5(a-3) - STAT6 gene

The Signal transducer and activator of transcription (STAT)6 gene have been mapped to chromosome 12q13.3–q14.1, and about 16.79 in length. There was no association between AD risk and the 2964 G > A SNP of the STAT6 gene while the 1315-GT repeat allele het erozygosity 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. [109] However, the short tandem repeat in exon 1 was not associated with AD risk in Chinese. [103] In Egyptian STAT6 2964 G/A and 2892 C/T polymorphisms were significantly associated with the development of AD. [101]

5(a-4) - IL-10 gene

IL-10 gene is located at chromosome 1q31-q32 and about 4.89 kb in length. The -1082A > G, -819T > C and -592A > C SNPs of the IL10gene did not contribute to the development of AD in Macedonian, and in German. [97] Also, -7616AGG promoter, -6365C > G 3526A > T, -795G>A, -1328 C>T, -2127 G>C, 3976 A>G and – 4311T>C SNPs of the IL10 gene were not associated with AD in German. [106,109] Whereas-1082A/G, -819C/T, and -

592A/C were significantly associated with atopic AD in Czech population. [102]

5(a-5) - IL-6 gene

IL-6 is located at chromosome 7p21 and about 6.12 kb in length. No association was found between the -174C > G SNP of the IL6 gene and AD. [106] As well as the -174C > G and -922A > G SNPs were not found. [106] Whereas -174C/G and nt565A/G were found that significantly associated with atopic AD in a Czech population. [102]

5(a-6) - TNF-α gene

Tumor necrosis factor (TNF)-α gene is located at chromosome 6p21.3. No significant association was found between -308 G > A SNP of the TNFα gene and AD in English. [110] 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. [103] Whereas, no association was not found between AG cdn25 and AD in population of Macedonians. [104]

5(a-7) - TNF-β gene

Tumor necrosis factor (TNF)-β is located at chromosome 6p21.3. No association was found between AD and -238G >A or -308G > A SNPs of the TNFβ gene in a German. [106]

5(a-8)- IL-1α gene

Interleukin (IL)-1α gene is located at chromosome 2q14 and about 11.48 kb in length. The -899T > C SNP of the IL1A gene was not associated with AD in Macedonians. [104]

5(a-9) - IFNγ gene

Interferon gamma (IFNγ) gene is located at chromosome 12q14and about 16.25 kb in length. Study on a Chinese population was demonstrated no association between short tandem repeats at the first intron of IFNγ gene and AD. [103] In addition, no association was found between 874 A>T IFNγ gene and AD in population of Macedonians. [104]

5(a-10) - IL-β gene

IL-1β is located at chromosome 2q14 and about 7.16 kb in length. No association was found between either the -511C > T, 3953T > C, 3953T > C, -1418T > C or the 315T > C SNPs of theIL1B gene and AD in American, German, English and Macedonians. [104,106,110]

5(a-11) - IL1RN gene

Interleukin 1 receptor antagonist **(**IL1RN) gene is located at chromosome 2q14.2 and about 34.70 kb in length. 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. [106]

5(a-12) - IL1RL1 (or ST2) gene

Interleukin 1 receptor-like 1 (IL1RL1) is located at chromosome 2q12 and 40.54 kb in length. A significant association between AD and the -26999G > A or SNP of the suppression of tumorigenicity (ST)2 gene was found in a Japanese population. [111] On other hand, 2992C > T, 5283G > A, 5860C > A, 11147C > T, 744C > A and -27639A > G SNPs were not 5q31.1 associated with AD risk. [111]

5(a-13) - IL-5 gene

IL-5 is located at chromosome and about 2.08 kb in length. The -703C > T SNP of IL5was not significantly associated with AD in Japanese. [112]

5(a-14) - IL-12 β gene

IL-12 β is located at chromosome 5q31.1-q33.1 and about 15.69 kb in length. The AA genotype of IL12B 1188A > C SNP was associated with decreased risk of AD in a Japanese population [113]. The 4237 G > A, 4496A > G and 4510G > A SNPs of theIL12B gene were not associated to the development of AD. [103] In addition 30 untranslated region of the IL-12B gene was associated with the AD phenotype. [113]

5(a-15) - IL-12R β

Interleukin12 receptor beta (IL-12R β) is located at chromosome 19p13.1 and about 39.94 kb in length. 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 and the TT genotype of the -2C > T SNP were significantly associated with an increased risk of AD in a Japanese population. [114]

5(a-16) - IL-13 gene

IL-13 is located at chromosome 5q31 and about 4.85 kb in direct. No association between the -1111C > T SNP of IL13and AD in Chinese population [103] and Japanese population. [115] While significant association between the -1024C > T SNP of the IL13 gene and AD was confirmed in German. [116] In the Japanese population there was no significant association between two SNPs of 704A > C and 1103C > T whereas the Arg allele of Arg144Gln SNP was significantly associated with an increased risk of AD in Japanese. [115] As well as the Arg 130 Gln polymorphism was confirmed in Canadian, [117] German, [116] and Japanese. [115] The A allele of the Arg144Gln SNP was associated with AD in German. [118] In Caucasians, haplotypes consisting of IL13 Arg144Gln with AD were associated with AD. None of the three SNPs (-1111C > T, 1293C > T, and Arg144Gln) were associated with AD during the first year. [106]

5(a-17)- IL-18 gene

IL-18 is located at chromosome 11q22.2-q22.3 and about 21.61 kb in length. Among five SNPs (-132A > G, -133C > G, -137G > C, -113T > G and 127C > T), only the C allele of the -137G > C SNP was associated with an increased risk of AD. [119]

5(a-18) - TGF-β1 gene

Transforming growth factor β1 (TGF-β1) is located at chromosome 19q13.2 and about 52.34 kb in length. The C allele of the TGF-β1 915 G > C SNP was associated with an increased risk of AD in British, whereas there was no significant difference in the frequencies of the 869T > C genotypes [120]. No association between AD and the -590C > T SNP was not found. [106]

5(a-19) - GM-CSF gene

Granulocyte macrophage colony-stimulating factor (GM-CSF) is located at chromosome 5q31.1 and about 2.38 kb in length. 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 British. [110] Although -1916T > C SNP was significantly associated with an increased risk of AD, there was a strong linkage disequilibrium existed between the -677A > C and -1916T > C SNPs. [110] The 3606T > C and 3928C > T SNPs of the GM-CSF gene was not associated with susceptibility to AD in Japanese. [121] While a strong linkage disequilibrium between 3606T > C and 3928C > T SNPs of the GM-CSF with AD in Canadian. [117]

5(a-20) - IL-9 gene

IL-9 is located at chromosome 5q31–35and about 4 kb in length.4091G>A of IL-9 gene polymorphism was associated with an increased susceptibility to Korean AD. [122]

5(a-21) - IL-9R gene

Interleukin 9 receptor (IL-9R) is located at chromosome Xq/Yq. 1737C/T gene polymorphism seems to be associated with an increased risk for developing non-allergic Korean AD. [122]

6 (b) - Chemokines and related genes:

Chemokines are classified into four classes on the basis of their protein structure: CXC (16 chemokines), CC (28 chemokines), C (2 chemokines), and CX3C chemokines (1 chemokines). [123] The CC and CXC chemokines are belong into inflammatory chemokines while the C and CX3C chemokines are belong to immune chemokines. Some chemokines, such as CCL5 (RANTES), CCL11 (exotoxin), CCL2 (MCP-1), CCL13 (MCP-4), CCL7 (MCP-3), CCL8 (MCP-2), and macrophage inflammatory protein (MIP)-1α CCL3, lead to cellular activation and inflammatory mediator secreted by basophils and eosinophil's. Several receptors have been shown to bind the chemokines: CCR Receptors for CC chemokine; CXCR receptors for CXC chemokines; XCR1 receptor for C and CX3CR1 receptor for CX3C chemokines. [123] At least three chemokine receptors have been demonstrated to mediate the recruitment of Th2 cells: CCR3, the receptor for CCL5 (RANTES), CCL11 (exotoxin), CCL2 (MCP-1), and CCL13 (MCP-4), which is also secreted in eosinophils and basophils, CCR4, the receptor for CCL17 (TARC), CCL22 (MDC) and CCR8, the receptor for CCL1 (I-309). Enhanced levels of both CCL5 (RANTES) and CCL11 (exotoxin 1) have been determined in the sera of AD patients, [124] with CCL5 (RANTES) signifying a crucial correlation with both total serum IgE levels and eosinophil numbers. Exotoxin 1 also has shown a high pattern of gene expression with AD patients. [125]

5(b-1) - CCL5 gene (or RANTES)

Chemokine (C-Cmotif) ligand 5 (CCL5) gene is located at chromosome 17q11.2- q12 and about 9.01 kb in length. Two polymorphisms in the CCL5 (RANTES) promoter region (-28CG and -403 GA) increase CCL5 (RANTES) expression in humans. [126] Indeed, these two (-28CG and -403 GA) CCL5 polymorphisms have been associated with susceptibility to AD patients. [127] In addition, the -401 G > A polymorphism has been shown a significantly frequency in AD patients among German population. In contrast, other study was not confirmed such as these association between (-28C > G, -403 G > A and -2518A > G) CCL5 polymorphisms with AD patients among Hungarian population. [128]

5(b-2) - CCL11 (or Exotoxin 1) gene

Chemokine(C-Cmotif) ligand 11 (CCL11) is located at chromosome 17q21.1- q21.2 2 and about 66 kb in length. In spite of multiple polymorphisms have been identified in the gene, only the two polymorphisms (-426C > T, -384A > G) were associated with serum IgE levels in Japanese AD. [129]

5(b-3)- CCL17 (or TARC) gene

The Chemokine(C-Cmotif) ligand 17 (CCL17) or thymus and activation-regulated chemokine (TARC) levels expression of AD patients were associated with disease activity. [130] In spite of some CCL17 polymorphisms are candidates as a genetic factor in AD, no correlation between AD and the -431C > T SNP of the CCL17 gene was found in a Japanese population. [131]

5(b-4)- CCR3 gene

Chemokine (C-Cmotif) receptor3 (CCR3) gene is located at chromosome 3p21.3 and about 143.70 kb in length. As mentioned before, CCR3 is a receptor for different chemokines which are play important role in AD pathogenesis. Hence, the biological activities of CCR3 suggest that polymorphisms of CCR3 may be an increased risk for AD. There was no significant difference in genotype frequencies of 51T > C SNP of the CCR3 gene between AD patients and controls among Japanese. [131]

5(b-5)- CCR4 gene

Chemokine (C-Cmotif) receptor-4 (CCR4) gene is located at chromosome 3p24 and about 3.36 kb in length. One study was not demonstrated a significant association between the 1014C > T CCR4 polymorphism and AD patients. [132]

5(b-6)- CMA1 gene

Mast cell chymase 1 (CMA1) gene is located at chromosome 14q11.2 and about 2.91 kb in length. A family-based association study in Caucasians revealed a significant association of this polymorphism with total IgE levels in patients with self-reported AD. [133] A significant association between the CMA1-1903A > G polymorphism and AD was observed by Weidinger et al. [134] It may be speculated whether this DNA variant alters the expression of chymase. It has also been shown that CMA1 is increased in chronic atopic eczema skin lesions [135] and a potential role of chymase in the promotion of skin barrier defects and cutaneous neovascularization has been suggested. [136]

6- Drug-metabolizing genes:

The metabolism of xenobiotic involves oxidation, reduction, and hydrolysis (phase I) and conjugation (phase II) reactions.

6(a-1)- GST genes

Certain genes within the glutathione S-transferase (GST) M, GSTT and GSTP subfamilies (GSTM1, GSTT1and GSTP1) are polymorphic in humans and the levels of individual enzymes expressed can be influenced by induction and genetic polymorphism. The GSTM1, GSTT1and GSTP1genes are located on chromosomes 1p13.3, 22q11.23 and 11q13, respectively. The 1404A > G (Ile105Val) and 2294C > T (Ala114 Val) SNPs of the GSTP1 gene were associated with a significantly increased risk of AD in Russian. [137]

6(a-2)- NAT-2 gene

N-acetyl transferase (NAT)2 gene is located at chromosome 8p23.1-p21.3and about 9.97 kb in length. N-acetylation is an important genetic polymorphic pathway in the biotransformation of one or more single-based mutations in the NAT2 gene known to cause low expression levels of functional NAT2 enzyme. 481C > T (synonymous mutation) and

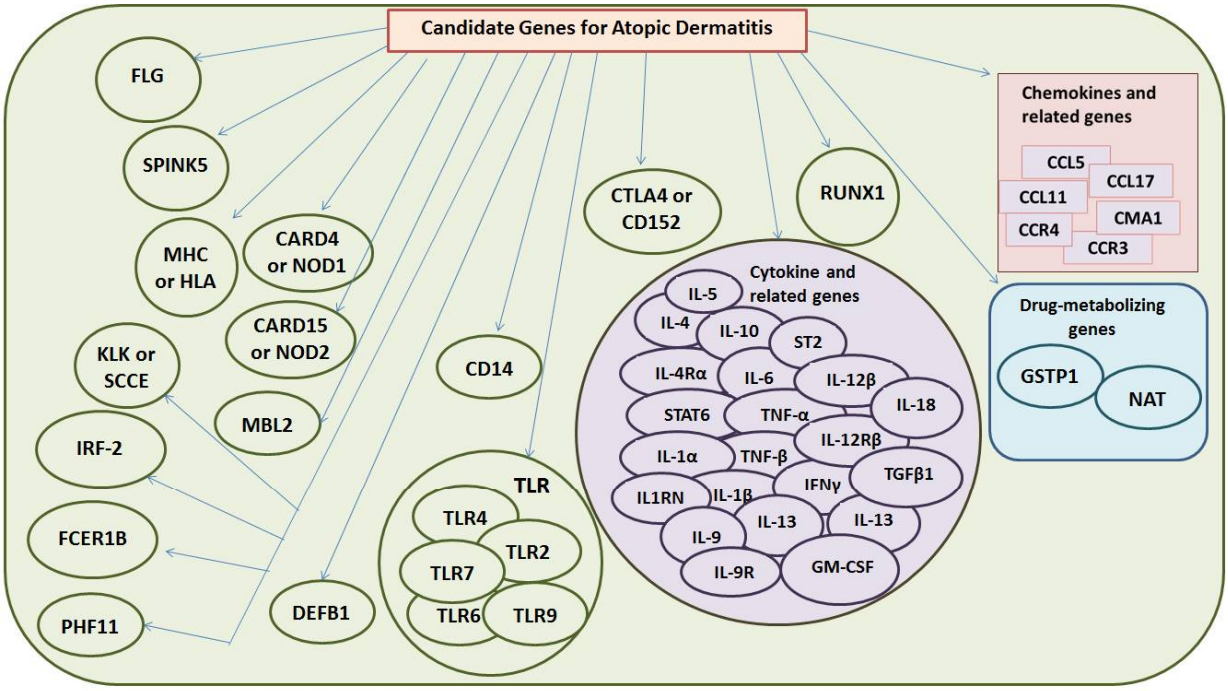

Figure 2. Identified candidate genes in atopic dermatitis. FLG, Filaggrin; SPINK5, Serine Protease Inhibitor Kazal-Type 5 ; MHC, major histocompatibility complex; HLA, human leukocyte antigen; CARD4, Caspase recruitment domain-containing protein 4; NOD, nucleotide binding oligomerization domain protein; CD, cluster of differentiation; MBL2, mannose binding lectin-2; TLR, toll like receptor; DEFB1, human defernsin 1; IL, interleukin; IL-4Rα, interleukin 4 receptor alpha; STAT6, signal transducer and activator of transcription-6; TNF, tumor necrosis factor; IFNγ, interferon gamma; IL1RN, interleukin 1 receptor antagonist; ST2, suppression of tumorigenicity-2; TGF, transforming growth factor; GM-CSF, granulocyte macrophage colony stimulating factor; CCL, chemokine C-motif ligand; CCR, chemokine C motif receptor; CMA1; mast cell chymase 1; GSTP1, clutathionine S-transferase P1; NAT, N-acetyl transferase; CTLA4, cytotoxic T-lymphocyte associated antigen-4; KLK, kallikrein; RUNX1, runt-related transcription factor 1; TRF-2, interferon regulatory factor 2; FCER1B, high affinity IgE receptor beta chain; PHF11, plant homeodomain zink finger 11 protein 11.

590G > A SNPs were not correlated with susceptible to AD in Russian. [138] Moreover, 481C > T, 590 G >A or 857G > A, were not associated with an increased risk of AD in Caucasian. [139]

7- Other genes associated with atopic dermatitis

7(a-1)- CTLA-4 (or CD152) gene

Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) gene is located at chromosome 2q33 and about 5.55 kb in length. CTLA -4 is associated to an increased the risk of autoimmune diseases. While, the 49A > G SNP of CTLA-4 gene was not associated with AD in Chinese. [140]

7(a-2)- KLK (or SCCE) gene

Kallikrein (KLK) or stratum corneum chymotrypsin enzyme (KLK) gene is located at chromosome 19q13.33 and about 7.57 kb in length. A significant genetic association was found between the rare AACCAACC variant of the KLK7 gene and AD in British. [141]

7(a-3)- RUNX1 gene

Runt-related transcription factor1 binding site between solute carriers (RUNX1) gene is located at chromosome 21q22.3. There was no significant allelic association between the RUNX1 polymorphism (rs734232) and AD in a small Japanese adult population. [142]

7(a-4)- IRF2 gene

Interferon regulatory factor 2 (IRF2) gene is located at chromosome 4q35. IRF-2--829C>T, -830C>T, -684C>T,-467G>A, one silent mutation in exon 9 (921G>A), and a 10-bp deletion in the 3' untranslated region (1739[ATCCC]8>6) polymorphisms were

significantly associated with atopic AD in Japanese. (143)

7(a-5)- FCER1B gene

High affinity IgE receptor beta chain (FCER1β) is located at chromosome 11q13. RsaIin2, RsaIex7 polymorphisms were significantly associated with atopic AD in British. (144)

7(a-6)- PHF11 gene

Plant homeodomain Zink finger 11 (PHF11) gene is Located at 13q14. T/C intron3, G/A 3UTR polymorphisms were significantly associated with atopic AD in Australian. (145)

Conclusions

Immune system plays a key role in the pathogensis of atopic dermatitis, therefore it is important to design an appropriate epidemiological investigation of immune system polymorphism for atopic dermatitis patients. Continued advances in molecular genetics and in high-throughput of genotyping methods will facilitate the analysis of multiple polymorphisms within genes and the analysis of multiple genes pathways. The effects of polymorphisms are best represented by their haplotypes. Data from multiple polymorphisms within a gene can be combined to create haplotypes and the set of multiple alleles on a single chromosome. Polymorphisms, even those not significantly associated with AD, should be considered as potentially important public health issues. In addition, it is important to keep in mind that a susceptibility factor in one population may not be a factor in another. There are differences in the prevalence rates of immune system polymorphisms among populations. In a population where the frequency of an “at-risk” genotype in a given polymorphism is too low, the “at-risk” allele or “at-risk” genotype can be rare to assess its associated risk.

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