Indonesian Journal of
Tropical and Infectious Disease
Vol. 3. No. 2 April–Juni 2012

Research Report

ETHNIC AND ATOPIC DERMATITIS: WHAT HAVE WE LEARNED IN ASIAN POPULATION?

Cita Rosita Sigit Prakoeswa
Dermato-Venereology Department
Medical Faculty Universitas Airlangga / Dr Soetomo Hospital
Surabaya - Indonesia

ABSTRACT

Atopic Dermatitis (AD) is a chronic inflammatory skin disease, with relapsing remitting course. Management of AD is challenging due to the complexities of this disease. Two hypotheses concerning the mechanism of AD have been proposed. One holds that the primary defect resides in an immunologic disturbance that causes Ig E-mediated sensitization, with epithelial barrier dysfunction regarded as a consequence of the local inflammation. The others propose that an intrinsic defect in the epithelial cells leads to the barrier dysfunction; the immunologic aspects is considered to be an epiphenomenon. Many studies support that AD is a complex trait which has interactions between genes and environmental factors contributing to disease manifestation, but the result of replicate association between genetic markers and AD is inconsistence. An important factor contributing to this inconsistency is related to population diversity. It is possible that certain genetic markers might contribute to increase the risk in certain ethnic population but not in others, either because of the differences in frequencies of the risk alleles and the specific genes interaction. There is limited information about the role of ethnicity in Asian population. The overall purpose of this review is to present an update on ethnicity approach of AD in Asian population. Research on prevalence, risk factor, innate and adaptive immune response genes, skin barrier dysfunction genes and gene-environment interaction such as epigenetic, is discussed. It is generally approved that the ethnicity of study subject is a key factor in interpreting genetic polymorphism studies. Therefore, discussion of some current areas of research about polymorphism are presented, including filaggrin (FLG) gene and CD14 C-159TSNP. Addressing the issues described above may improve our understanding of AD pathogenesis that has implications for the clinical management of AD.

Keywords: *Atopic Dermatitis, ethnic, Asian, immune system, skin barrier, gene-environment interaction*

ABSTRAK

Latar Belakang: *Dermatitis Atopik (DA) merupakan penyakit keradangan kulit yang bersifat kronis dengan periode remisi dan eksaserbasi. Kompleksitas dari penyakit tersebut menjadikan tantangan bagi Dokter Spesialis Kulit dan Kelamin dalam melakukan penatalaksanaan. Patogenesis DA didasari oleh dua hipotesis. Pertama, gangguan imunologi sebagai penyebab primer, menyebabkan sensitisasi yang diperantarai oleh Ig E, selanjutnya terjadi kerusakan barrier kulit sebagai konsekuensi dari keradangan local yang terjadi. Kedua, gangguan primer pada sel-sel epitel kulit menimbulkan disfungsi kulit sebagai barrier, sehingga memudahkan terjadi keradangan dan diikuti dengan proses imunologi. Berbagai penelitian mendukung kontribusi interaksi antar gen serta lingkungan sebagai factor penting dalam manifestasi klinis DA, tetapi asosiasi antara petanda genetic dan DA masih inkonsisten. Faktor penting yang berkontribusi pada hal tersebut adalah diversitas populasi. Petanda genetic tertentu dapat berperan untuk meningkatkan resiko terjadinya DA pada populasi etnik tertentu karena adanya perbedaan frekuensi alel dan interaksi spesifik berbagai gen. Informasi tentang peran etnisitas pada populasi Asia sangat terbatas.* ***Tujuan:*** *dari penulisan ini adalah untuk menggambarkan pendekatan terkini tentang etnis pada DA di populasi Asia. Diskusi meliputi penelitian yang telah dilakukan tentang prevalensi, factor resiko, gen yang bertanggung jawab pada respon imun alami maupun adaptif, gen yang bertanggung jawab pada disfungsi barrier kulit serta interaksi antara gen dengan lingkungan seperti epigenetic. Secara umum disepakati bahwa etnisitas subyek penelitian merupakan faktor kunci dalam interpretasi penelitian polimorfisme. Oleh karena itu, penelitian polimorfisme termasuk gen penyandi filaggrin*

dan CD 14 C-159T juga dibahas pada tulisan ini. Pemahaman tentang pathogenesis DA diharapkan dapat meningkatkan kualitas penatalaksanaan klinis DA.

Kata kunci: *Dermatitis Atopik, etnik, Asia, sistemimun, barrier kulit, interaksi gen - lingkungan.*

INTRODUCTION

A topic dermatitis (AD) is a common inflammatory skin disease that may affect individuals in any age, race, or ethnicity. It is commonly affected during childhood or infancy with chronic and relapsing course. The etiology of AD is partially understood, genetics and environmental factors are thought to play important roles in the pathogenesis.[1]

Asia is the largest continent in the world and has many different geographic areas. It extends from countries in the sub tropic zones, the Far East (including Japan, Korea, and China) to countries in the tropics, the South and Southeast Asian countries (including Singapore, Malaysia, the Philippines, Indonesia, Thailand, Vietnam, Cambodia, Laos, and Myanmar) and to countries in the subtropics (including the Indian subcontinent and countries in the Middle East). Most of the Asian population has Fitzpatrick skin photo type III, IV, and V, whereas a small proportion has skin photo type II and VI. Wide variety of different ethnicity, culture, hygiene, nutrition, and socioeconomic status also present. The manifestation of dermatologic conditions in one part of Asia is commonly different from those seen in another part.[2]

Racial differences in both the expression of AD and genetics are important areas of research for several reasons. First, there might be different phenotypic expression of the disease in a given racial and or ethnicity group (that might or might not be confounded by environmental differences). Secondly, the frequency of genetic variation varies between races.[3]

Ethnic (racial) differences in AD have been minimally investigated. The current experimental human model for skin is commonly based upon physical and biochemical properties known about Caucasian skin. Thus, anatomical or physiological properties in skin of different races may influence a disease process or a treatment of that disease it self. There is limited information about the role of ethnicity in Asian population.[4]

The overall purpose of this review is to present an update on several approaches to understanding the susceptibility and expression (severity) of AD in Asian population. **Four key questions are addressed in this review: (1) What is the difference between race and ethnic? (2) Do the biophysical properties of Asian skin differ from others? (3) Are there any differences between prevalence and risk factor of AD in Asians and others? (4) What about the research on innate and adaptive immune response genes, skin barrier dysfunction genes and gene-environment interaction such as epigenetic of AD based on ethnicity in Asians?**

QUESTION 1: What is the difference between race and ethnicity?

Definitions of ethnicity and race based on New Oxford American Dictionary are:[5]

Ethnicity is the population subgroup (within a larger dominant national or cultural group) with a common national or cultural tradition.

Race is each of the major divisions of human-kind, having distinct physical characteristic. Race also means a group of people with common features.

QUESTION 2: Do the biophysical properties of Asian skin differ from others?

Racial variability should be considered in terms of different skin responses to topical and environmental agents. Race provides a useful implement to investigate and compare the effects of lifetime sun exposure and ambient relative humidity. Evolution provided over 100,000 years of genetic advantage to survive for those races living in a specific area with specific climatic conditions. To survive in harmful environment requires an optimal adaptation of outermost layers of our body, the skin relates to structural, biochemical, and molecular level.[4]

Stratum Corneum (SC) is equally thick in different races. However, Weigand demonstrated that the SC in blacks contained more cell layers and required more cellophane tape strips to be removed than the SC of Caucasians, while Kampaore and Tsuruta showed that Asian skin was significantly more sensitive tostrip than black skin. No correlation was found between the degree of pigmentation and the number of cell layers. These data clarified that the greater intercellular cohesion in blacks, consequences in an increased number of cell layers and an increased resistance to stripping. This mechanism may involve lipids, because the lipid content of the SC ranges from 8.5% to 14%, with higher values in blacks.[4]

Corcuff investigated the corneocyte surface area and the spontaneous desquamation and found no differences between black, white, and oriental skin. However, an increased desquamation (up to 2.5 fold) was found in blacks. They concluded that the differences might be related to a different composition of the intercellular lipids of the SC.[6] Sugino found significant differences in the amount of ceramides in the SC, with the lowest levels in blacks followed by Caucasians, Hispanics, and Asians. In this experiment, ceramide levels were inversely correlated with transepidermal water loss (TEWL) and directly correlated with water content.[7] Meguro confirmed these correlations.[8] These data may partially explain the controversial findings in the literature on the mechanisms of skin sensitivity. Changes in skin permeability and barrier

function have been reported. Kompaore evaluated TEWL and lag time after application of a vasoactive compound (methyl nicotinate) before and after removal of the SC by tape stripping. Before tape stripping, TEWL was 1.3 times greater in blacks and Asians compared to Caucasians. No difference was found between blacks and Asians, whereas after stripping they found a significantly higher TEWL in blacks and Asians than in Whites. In particular, after stripping Asians showed the highest TEWL (Asians 1.7 times greater than Caucasians).[9,10] They concluded a resemblance with previous studies,[11,12] which concluded that skin permeability measured by TEWL, was higher in blacks than in Caucasians. They also concluded that Asian skin had the highest permeability among the study groups. However, these findings have not yet been confirmed by other groups. Infact, Sugino, that also included Asians in their study found that the baseline TEWL decreased, blacks were greater than Caucasians greater than or equal to Hispanics and greater than or equal to Asians.[7] Another study about Asian skin, has compared the TEWL between Asians and Caucasians and found no statistically significant difference at baseline or after tape stripping without vasoactive substance applied.[13] Reed found differences in the recovery of the barrier between subjects with skin type II/III compared to skin type V/VI, and no differences between general Caucasians and Asians.[14] Darker skin recovered faster after the barrier damage was induced by tape stripping.[4]

Racial differences in skin conductance are difficult to interpret in terms of SC water content, because other physical factors, such as the skin surface or the presence of hair, can modify the quality of the skin electrode contact. Volar and dorsal forearms present a significant differences between all races.[15] These results are apparently contrast with TEWL recordings. Indeed, increased SC water content, correlates with a higher TEWL.[16] These data may be explained on the basis of the differences of intercellular cohesion or lipid composition. The increasing of skin water content could possibly occur due to the greater cell cohesion with a normal TEWL.[4]

There are reasonable evidences that exist to support that black skin has a higher TEWL compared to white skin by means of objective measurements. Although some deductions have been made about Asian skin, the results are contradictive, and further evaluation of Asian skin needs to be performed. Perhaps, more specificity about the origin of their heritage should also be included because "Asian" encompasses a broad spectrum of people.[4]

QUESTION 3: Are there any differences between prevalences and risk factors of AD in Asian and others?

There are still limited studies available pertaining the epidemiologic data of AD in Asian populations. However, several population studies have demonstrated considerable geographic and racial/ethnic variations in the prevalence of AD.[18,19,20] Based on partially understood environmental factors, AD appears to be more common in industrialized nations and urban settings than in developing countries and rural communities.[21] Survey study about population in northern Europe, the United States, and Japan has reported prevalence rates of 15.6%, 17.2%, and 21%, respectively, whereas a prevalence of 8.5% was reported in a recent study from South Eastern Nigeria.[22,23,24,25] However, with expanded urbanization and adoption of Western lifestyle, the prevalence of AD appears to be rising in developing countries, as in more industrialized nations.[25] The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee evaluated the frequency of AD among 463,801 children aged 13–14 years old from 56 countries.[18] In 1999, high prevalence of AD was reported in several regions where non-Caucasian individuals predominated, the centers of Africa (Nigeria, Kenya), Asia (Japan, Pakistan), and of South America (Paraguay, Chile). Several epidemiologic studies have shown increasing prevalence of AD among blacks and Asian/Pacific Islanders when compared with Caucasians. Recently, a 12-month observational prospective study of 182 babies (62 Caucasian, 61 Chinese, and 59 Vietnamese infants) born in Melbourne, Australia, indicated that the incidence rate of AD was varied by ethnicity.[20] In those populations, AD prevalences of the Caucasian, Chinese, and Vietnamese infants were 21%, 44%, and 17% respectively. Because the Caucasian and the Chinese infants were in similar socioeconomical backgrounds, genetic differences likely played a role in the different incidence rates. In contrast, since the Vietnamese infants had a lower socioeconomic background, but were skill in the same racial group as the Chinese infants, environmental factors likely contributed more than genetic factors to these incidence differences.[20] AD was found to be more prevalent among Chinese infants born in San Francisco and Honolulu than among the local Caucasian population.[26] Similar findings were presented in London-born black Caribbean children compared with their white counterparts. Among London-born black Caribbean children, the prevalence of AD was 16.3% compared with 8.7% in white children.[19] However, a study of Indian and Caucasian preschool children in Leicester, United Kingdom, failed to show any ethnic differences in the prevalence of AD.[27] The reasons for the observed differences in prevalence may be based at least in part, on variations of genetic and environmental factors. However, differences of research methodology between epidemiologic studies must be considered when comparing prevalence rates among populations. Further research on the epidemiology of AD among Asians is warranted.[17]

A study about prevalence of AD by ethnic group was conducted by Baker in suburban area of San Diego. Ethnic the data were available for 5912 patients in the study population. Ethnicity was designated as white (not of Hispanic origin), Hispanic, black, Filipino, other Asian, or mixed race. The prevalence of AD was determined to be 3.2% in the overall study population, 3.7% of which were black, 8.5% were Filipino, 2.0% were Hispanic, 2.8% were

white (not of Hispanic origin), 3.2% were mixedrace, and 5.6% were other Asian origins.[28] Because this study was conducted by only one physician in a limited geographic area, it couldn't be assumed that the population study typically represents the overall Filipino population in the United States or in the Philippines. The actual prevalence of AD probably varies considerably by geographic area. Moreover, the population is not ethnically representative of the overall US population. In particular, although he observed a higher prevalence of AD among patients of "other Asian" origin, this group included too many subsets for separate analysis (ie, Japanese, Korean, Chinese, Laotian, Vietnamese, Cambodian, and other ethnic groups were included).[28]

A prospective study was undertaken to investigate several perinatal predictors of AD occurring in the first 6 months of life which were reported from 1005 mothers and their infants who participate in a US cohort study of pregnant women and their offspring. The main outcome measurement was maternal report of an AD diagnosis in the first 6 months of life and analyzed using multiple logistic regression models to assess the association between several simultaneous predictors and incidence of AD. The cumulative incidence of AD in the first 6 months of life was 17.1%. The adjusted odds ratio (OR) for risk of AD among infants born from black mothers was 2.41 (95% confidence interval [CI]: 1.47, 3.94), compared with infants born from white mothers, and was 2.58 (95% CI: 1.27, 5.24), compared with infants born from Asian mothers. Male infants had an OR of 1.76 (95% CI: 1.24, 2.51). Increased gestational age at birth was a predictor (OR: 1.14; 95% CI: 1.02, 1.27, for each 1-week increment), but birth weight for gestational age was not. Infants born by mothers with a history of AD had an OR of 2.67 (95% CI: 1.74, 4.10); paternal history of AD was also predicted, although maternal atopic history was more predictable than paternal history. Several other

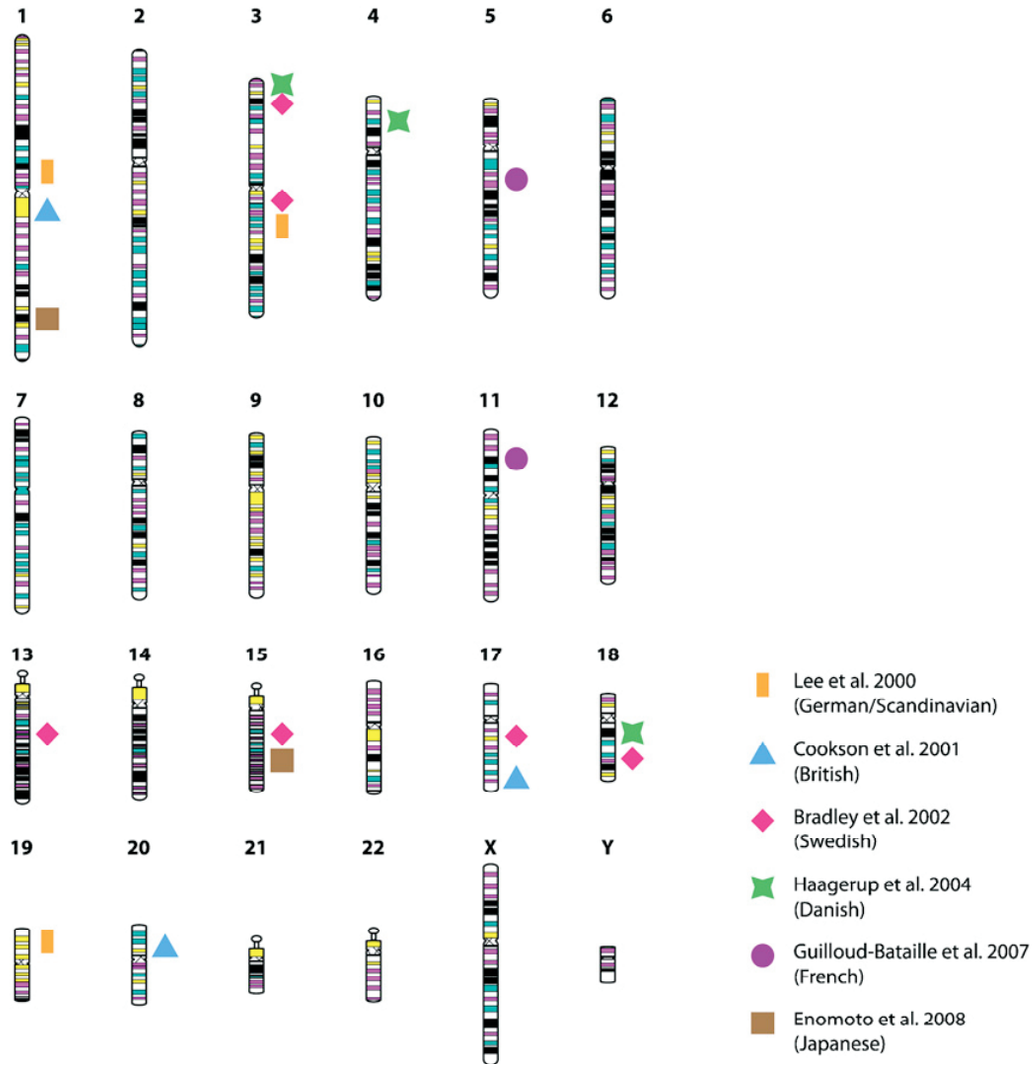

Figure 1. Summary of genome-wide linkage studies of AD: representation of the 23 human chromosomes, highlighting those loci for which genome screens have identified linkage to AD. Loci are mapped to short orlong chromosomal arms and color-coded according to the studies listed in the legend.[30]

perinatal, social, feeding, and environmental variables were not related to the risks of AD. In conclusion, Black and Asian race/ethnicity, male gender, higher gestational age at birth, and family history of atopy, particularly maternal history of AD, were associated with increased risk of AD in the first 6 months of life. These findings suggest that genetic and pre and perinatal influences the essential in the early manifestation of this condition.[29]

QUESTION 4: What about the research on innate and adaptive immune response genes, skin barrier dysfunction genes and gene-environment interaction such as epigenetic of AD based on ethnicity in Asians?

STRATEGIES FOR INVESTIGATING THE GENETIC BASIS OF ATOPIC DERMATITIS

A large amount of research have been undertaken worldwide in the exploration of genetic factors as the etiology of AD. Three main approaches have been used: candidate gene association, selecting genes for study based on a hypothesis of known biological function; genome-wide linkage screens, which are hypothesis free and compare the transmission of genetic information between cases and controls in family pedigrees; and DNA microarray studies, which look at gene expression in selected regions of interest, or across the whole genome. Each of these strategies has been added to the understanding of genetics in AD.[29]

Up to present, there have been 5 genome-wide linkage studies performed on AD, plus a genome-wide linkage screen originally designed for asthma with analyses repeated for the AD outcome (Fig 1). All but one of these screens were performed on families of European ancestry: (1) 199 German and Scandinavian (2) 148 British (3) 109 Swedish (4) 100 Danishand (5) 295 Frenchfamilies, of which 62 affected sib pairs for AD were available for reanalysis. The non-European study was performed on 77 Japanese families selected through 111 sib pairs with AD

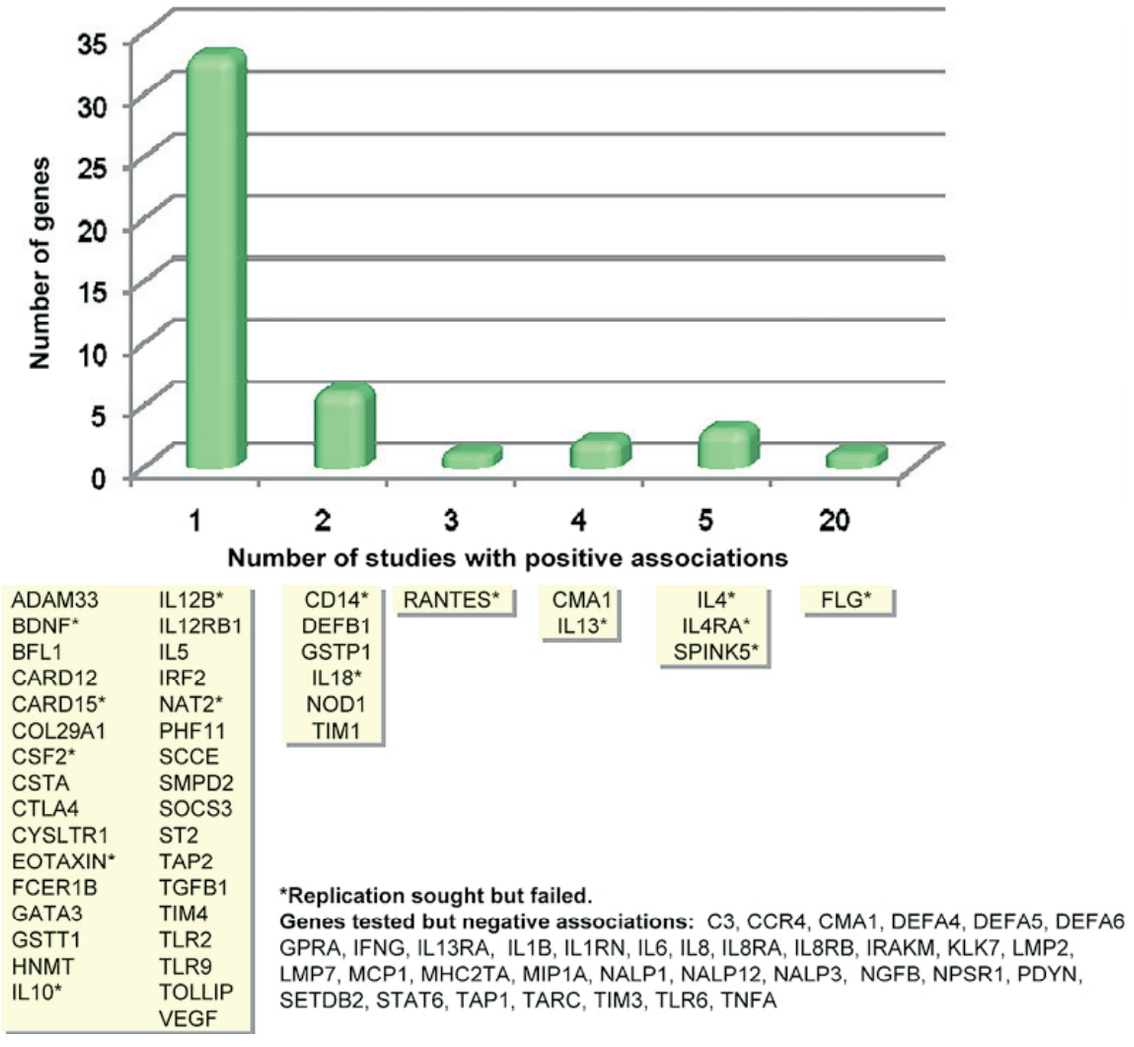

Figure 2. Genes associated with AD in at least 1 published study. Genes are grouped according to how many positive association studies have been reported. The y-axis indicates the number of genes (corresponding to the yellow boxes) for each time that a positive association was reported.[30]

(287 individuals) and relied on a linkage mapping panel of 5,861 single nucleotide polymorphisms (SNPs) rather than the microsatellite panel traditionally used for linkage screens. In the Japanese families, demonstrated linkage at two locus on chromosome 1 and 15 didn't show replication with other studies.[30]

In a search of the public database in June 2009, 111 studies were identified for which results of the tests associated to AD were reported on a candidate gene. The major outcome was limited to AD as a qualitative trait or AD severity. From these 111 published studies, only 42 studies were performed in Asian populations. There are reports on 81 genes, of which more than half (46 genes) had at least 1 positive association study reported (Fig 2). Of these 46 genes, 15 studies failed to replicate associations, and 13 were positively associated in at least 1 other independent study. One of these genes, FLG, has been associated with AD in 20 different reports. There are 35 additional genes studied for which there has been no evidence for a positive association to date.[30]

ADAPTIVE AND INNATE IMMUNE RESPONSE GENES

One approach toward distinguishing potential genes interactions and systematically evaluating the role of candidate genes/polymorphisms in AD susceptibility, for which there is compelling evidence for association, is to implement the program Ingenuity Pathways Analysis (Ingenuity Systems, Inc, Redwood City, Calif; www.analysis.ingenuity.com). As a proof of the concept, Barnes (2010) evaluated the 81 genes summarized in Fig 2 using the Ingenuity Pathway Analysis. There were slightly more than half (n = 48) of the 81 genes studied clustered in 2 major networks, both of which were associated with immune dysregulation, specifically the pathway which is associated with antigen presentation and cell-mediated and humoral immune response, the pathway associated with cell signaling and interaction cellular movement. Six genes (monocyte differentiation antigen CD14 [CD14], GATA-binding protein 3 [GATA3], interleukin 4 [IL4], IL18, nucleotide-binding oligomerization domain 1 [NOD1], and Toll-like receptor 2 [TLR2]), which had previously been significantly associated with AD, were clustered into the antigen presentation and immune response pathway. Meanwhile, 9 previously associated genes (BCL2-related protein A1 [BCL2A1], brain-derived neutrophilic factor [BDNF], Regulated upon Activation,Normally T-Expressed, and presumably Secreted [RANTES], colony stimulating factor 2 [CSF2], glutathione S-transferase P 1 [GSTP1], IL5, interleukin 12 beta [IL12B], interleukin 12 receptor beta 1 [IL12RB1], and suppressor of cytokine signaling 3 [SOCS3]) were clustered into the cell-signaling/movement pathway. Although the studies for which those candidates genes were evaluated did not specifically tested for genes interaction. This investigation potency serves as an example of the power of this approach in selecting optimal candidates for genetic association studies.[30]

In Asian population, there were three genes explored from the antigen presentation and immune response pathway (CD14, IL4 and IL18) and six genes from the cell-signaling/movement pathway (BDNF, RANTES, CSF2, IL5, IL12B, IL12RB1), from total of 42 studies. Barnes presented significant correlation between IL4 and IL18 and AD in Asian population. And also discovered significant correlation between BDNF, RANTES, IL5, IL12B and IL12RB1 in Asian population (Japanese, Chinese and Korean, table 1). Due to the minimal amount of studies study, these results have a limitation to make a conclusion about the role of SNP in there genes of AD from Asian population.[30]

On account of the historical isolation and environmental positive selections, major racial/ethnic groups differ in allele frequencies.[31] Consequently, ethnic differences may contribute to the variations in allele frequencies of phenotype-associated genes in humans. The CD14 protein, which is the receptor for lipopolysaccharides (LPS) and other bacterial wall-derived components, has been suggested to play a critical role in Th1 differentiation of naive T cells, with the likelihood of developing a T helper 1 (Th1)-type response by up-regulating the expression of IL-12, which in turn decreases IgE-mediated immunity.[32]Zhang reviewed the CD14C-159T SNP in the promoter region of CD14 in asthma population. There are significant variations in allele frequencies in different ethnic groups, summarizing that C allele frequencies on the highest in those of African descent, followed by Caucasians and Asians. This indicates that there are significant genetic variations between these ethnic groups in terms of predominant alleles and linkage disequilibrium structure of the SNP CD14C-159T. It is generally approved that the ethnicity of study subjects is a key factor in interpreting genetic polymorphism studies. In AD, there is an inconsistent result of studies of CD14C-159T SNP. There is significant association in American and German population, but not in German and Chinese population. Therefore, we still could not make a conclusion about the role of SNP CD14C-159T in AD from Asian population.[33]

SKIN BARRIER DYSFUNCTION GENES

It is increasingly appreciated that both genetic and environmental factors that affect skin barrier function contribute to AD susceptibility, as well as barrier dysfunction which is an essential feature of AD. A disrupted barrier would allow penetration of microbes and allergens and other environmental insults, such as toxins, irritants, and pollutants, with consequences such as inflammation, allergen sensitization, and bacterial colonization. Although the epidermis functions as the primary defense to the external environment, considerably barrier function is regulated by the SC and by the tight junctions (TJ), which reside at the level of the stratum granulosum. When the SC is compromised, either by the reduced levels of SC lipids, mechanical trauma resulting from extensive scratching that

is precipitated by intensive itch (the hallmark of AD), or as a result of genetic defects in SC proteins (ie, FLG), TJs are the next line of defense. Linkage screens performed on AD to date have not elucidated specific candidate genes per SC, but they have implicated loci harboring clusters of genes associated with skin barrier dysfunction. Specifically, one of the earliest screens indicated linkage at the epidermal differentiation complex (EDC) locus on chromosome 1q21, which contains a very large and diverse family of genes associated with skin barrier dysfunction, including loricrin, involucrin, members of the S100 gene family, and most notably, FLG.[34]Association studies on genes related to the EDC cluster and other barrier dysfunction candidates have been restricted to FLG, also known as filament-aggregating protein, and within FLG, most associations have been limited to 2 null mutations (R501X and 2282del4). In fact, FLG is the most consistently associated gene with risk of AD, as shown in Fig 2, by mid-2009, there were 20 positive reports on genetic associations between FLG mutations and AD.[35] The gene encoding human FLG was firstly cloned in 1989, when it was found to contain numerous tandem FLG repeats localized in chromosome 1q21, and because of its tight regulation at the transcriptional level in terminally differentiating epidermis, it was postulated to be an important candidate for disorders of keratinization.[36]It was subsequently evaluated for its function in the formation of the SC and found to be a critical protein involved in epidermal differentiation and in maintaining barrier function.[37] Full sequencing of the FLG gene has revealed multiple additional polymorphisms with varying frequency across the ethnic groups. However, with a combined allele frequency among patients with AD of 18% and 48% for the R501X and 2282del4 mutations respectively, the 2 null mutations represent the strongest and most compelling genetic risk factors for AD.[38]In the largest meta-analysis performed, that on the R501X and 2282del4 mutations, Rodriguez analyzed data from 24 independent studies, which included 6,448 cases, 26,787 control subjects, and 1,993 families (all selected forAD) and determined that the effect size's risk effect of eczema caused by the 2 FLG null mutations was not dissimilar to previous reports at an OR of just over 3.[39]

Other candidate genes showing somewhat comparable OR include IL-4, OR 1.88, $p = 0.01$[40]; IL-13, OR 1.7, $p = 0.03$[41] and relative risk (RR) 2.5, $p = 0.014$[42]; and mast cell chymaseOR 2.17, $p = 0.009$.[43]

Brown reviewed about genotype-phenotype correlation between FLG and AD, showed the phenotype of early onset (before the age of 2 years), persistent, and severe AD has shown the strongest and the most highly significant statistical association with the combined FLG null genotype, having an OR of up to 7.7 (95% CI 5.3–10.9).[44,45,46]

In Asian population three studies have been conducted to explore the SNP of FLGin AD from Japanese, all of these studies showed positive association (table 1). Further research are required to establish this finding.[30]

EPIGENETIC

Epigenetics is the study of mitotically heritable changes in phenotype (alterations in gene expression) that occur without direct alterations of the DNA sequence. These epigenetic changes include methylation of DNA by the covalent addition of a methyl group to a cytosine residue in a CpG site; posttranslational modification of the amino acid tails of histones by means of acetylation, phosphorylation, methylation and aberrant expression of microRNAs (miRNAs), each of which is capable of posttranscriptionally regulating the expression of a cohort of cognate target genes.[47]

DNA methylation requires the activity of DNA methyltransferases (DNMTs).The mechanism of DNA demethylation is less clear. Loss of binding to methylated DNA-binding proteins might allow the promoter to enter a transcriptional state.[47]

AD is a complex disease for which the risk is convinced to be determined by a complicated interplay of genetics and environmental exposures that have been discussed and debated for many years. The recent understanding of epigenetics as a mechanism mediating gene-environment interaction offers new opportunities to advance novel concepts and re-examine established ones about this disease.[29]

Ho reviewed regarding environmental epigenetics of asthma, including the epigenetic effects of tobacco smoke, microbial allergens, oxidants, airborne particulate matter, diesel exhaust particles, polycyclic aromatic hydrocarbons, dietary methyl donors and other nutritional factors, and dust mites. The discovery and validation of epigenetic biomarkers linked to exposure asthma, or both might lead to better epigenotyping of risk, prognosis, treatment prediction, and development of novel therapies.[47]

In AD, environmental factors, possibly react through epigenetic mechanism, and it may contribute to disease pathogenesis. In support of this, DNA Methyltransferase (Dnmt1) transcripts in peripheral blood mononuclear cells of AD patients with high IgE levels are significantly lower than the control.[48] The effect of reduced Dnmt1 level on IgE may be indirect, with DNA hypomethylation of T cells resulting in their increase production of IL4, which then stimulates IgE production by B cells.[49,50] Enhanced immune response at epidermal surfaces, caused by DNA hypomethylation of methylation-sensitive immune genes, along with the activation of the genes to critical to T/Bcells interactions and inflammation, could initiate a sustained immune response.[51]

Ho also reviewed the trigger factos that influence epigenetics of asthma. That finding in agreement with previous studies reporting that Benzopyrene(BaP)is able to decrease global DNA methylation, inhibit Dnmin vitro, and interfere with recruitment of the methylation machinery. BaP is frequently used as a prototype Polycyclic Aromatic Hydrocarbon (PAH) for many experimental studies. In

Asthma, (PAHs) are one of the most widespread classes of pollutants of the environment and in food. They are present in crude oil, coal, and tar deposits and are derived from incomplete combustion of fossil fuel, oil, garbage, and cigarettes. They are major components of airborne particulate matter (PM) of urban aerosols and widely exist in food products, including grains, vegetables, oils, and fats. PAHs are emitted to the air during the production of coke and aluminum. Cooked meats are contaminated when they are charcoal grilled, roasted, or smoked.[47]

The trigger factor that could reduce Dnmt1 in AD is still unknown, it is possible that BaP has a role in AD as stated above, further studies are required.

SUMMARY

An important factor contributes to the failure of reproducing associations between genetic markers and a complex trait, such as AD, in independent populations is also related to population diversity. It is possible that certain genetic markers might contribute to disease risk in a particular (ie, ethnic or racial) population but not in others, either because of differences in frequencies of the risk alleles or because of specific genes interactions. It is still difficult to evaluate the effect of ethnicity on genetic associations of AD in Asian population, because however, there is relatively little diversity in the populations that have been studied.

FLG is probably the best example of a candidate gene for which ethnicity likely influences the extent to which a polymorphism confers risk. In relevance to clinical practice, individuals with FLG insufficiency are at increased risk of severe and persistent AD, which future therapy may place greater emphasis on barrier repair for this subgroup of patients. AD is a disease in which pharmacogenetics may facilitate the development of primary prevention and treatment regiments tailored according to the individual genetic predisposition in Asian population.

Table 1. Genes associated with atopic dermatitis in at least one study based on ethnicity in Asian population[30]

Gene	Chromosomal location	Variant	Association	Population	No. of subjects*
ADAM33	20p13	rs2853209	Yes	Japanese	140/258
BDNF	11p13	C270T	Yes	Chinese	160/169
CCR4	3p24	C1014 T	No	Japanese	198/183
CD14	5q31.1	C-159T/C-260T	No	Chinese	171/160
			No	Chinese	113/67
CMA1 (MCC)		BstXI	Yes	Japanese	100/100
			Yes	Japanese	145/706
			No	Japanese	100/101
			Yes	Japanese	169!
CSF2	5q31.1	T3606C	No	Japanese	181/100
DEFA4	8p23.1	G-6298C	No	Korean	631/458
DEFA5	8p23.1	G-2819A	No	Korean	631/458
DEFA6	8p23.1	G-4844A	No	Korean	631/458
DEFB1	8p23.1	T-2266C	Yes	Korean	631/458
EOTAXIN(CCL11)	17q21.1-q21.2	C-426 T	No	Japanese	140/140
			No	Japanese	140/140
		A-384 G	No	Japanese	140/140
			No	Japanese	140/140
		G67A	No	Japanese	140/140
			No	Japanese	140/140
FLG	1q21.3	R501X, 3321delA, S1695X, Q1701X, S2554X,			
S2889X, S3296X	Yes	Japanese	118/134		
		S2554X	Yes	Japanese	105 families, 376/923
		S2554X, S2889X, S3296X, and 3321delA	Yes	Japanese	125/133
IFNG	12q14	STR at first intron	No	Chinese	94/186
IL4	5q31.1	C-589T (C-590 T)	Yes	Japanese	88 families
			No	Japanese	302/122
			No	Chinese	94/186

Table 1 Continuation.

Gene	Chromosomal location	Variant	Association	Population	No. of subjects*
		C-3112 T	Yes	Japanese	202/150
		T33C	No	Chinese	94/186
IL4RA	5p13	C-703 T	Yes	Japanese	451/116
		Ile50Val	No	Japanese	27/29
			No	Japanese	302:122
		A184G	No	Japanese	202/150
		G186A	Yes	Japanese	
		A326C	Yes	Japanese	
		C327A	Yes	Japanese	
		Glu375Ala	No	Japanese	27/29
			No	Japanese	302/122
		E375A	No	Chinese	94/186
		L389L	No	Chinese	94/186
		Cys406Arg	No	Japanese	27/29
		C406R	No	Chinese	94/186
		S503P	No	Chinese	94/186
		Glu 551Arg	Yes	Japanese	27/29
			No	Japanese	302/122
		Q576R	No	Chinese	94/186
		T1803C	Yes	Japanese	202/150
		C3112 T	Yes	Japanese	202/150
IL5	5q31.1	24597T/A	Yes	Korean	646/474
IL5R	3p26-p24	28380C/A	No	Korean	646/474
IL8	4q12-q13	2352A/T	No	Korean	646/474
IL8RA (CXCR1)	2q35	3047C/T	No	Korean	646/474
IL8R (CXCR2)	2q35	L262L	No	Korean	646/474
IL10	1q31-q32	A-1082 G	No	Korean	276/140
			No	Chinese	94/186
		T-819C	Yes	Korean	276/140
			No	Chinese	94/186
		A-592C	Yes	Korean	276/140
			No	Chinese	94/186
IL12B	5q31.1-q33.1	A1188C	Yes	Japanese	164/100
		G4237A	No	Chinese	94/186
IL12RB1	19p31.1	A-111 T	Yes	Japanese	382/658
IL13	5q31	C-1112T	No	Chinese	94/186
		A704C	No	Japanese	185/102
			No	Japanese	185/102
		C1103T	No	Japanese	185/102
			No	Japanese	185/102
		G4257A	Yes	Japanese	185/102
			Yes	Japanese	185/102
		G4464A	No	Chinese	94/186
		T7488C	No	Japanese	160/103
IL18 (IGIF)	11q22.2-q22.3	T113G	Yes	Korean	646/474
		G2137C	No	Japanese	160/104
IRF2	4q35.1	C-829T (C-830 T)	No	Japanese	49 families
LMP2	6p21.3	LMP2*R	No	Korean	53/184
LMP7	6p21.3	LMP7*A	No	Korean	53/184
MIP1A (CCL3)	17q12	C954T	No	Japanese	39/65
RANTES (CCL5)	17q11.2-q12	G-401A	Yes	Japanese	62/14
			Yes	Japanese	389/177
			Yes	Japanese	389/177
SMPD2	6q21	Haplotype	Yes	Korean	284/248
SPINK5 (LEKTI)	5q32	G-206A	Yes	Chinese	669/711
		Asp106Asn 41	No	Japanese	families

Table 1 Continuation

Gene	Chromosomal location	Variant	Association	Population	No. of subjects*
			Yes	Japanese	124/110
			Yes	Japanese	41 families
			No	Japanese	124/110
			No	Japanese	41 families
		His396His	Yes	Japanese	124/110
		Glu420Lys	Yes	Japanese	124/110
			Yes	Japanese	118
			Yes	Japanese	41 families
		Glu420Lys	No	Chinese	669/711
		Glu825Asp	No	Japanese	41 families
		A1103G	No	Chinese	669/711
		G1156A	No	Chinese	669/711
		G2475 T	No	Chinese	669/711
		IVS12-26C/T	Yes	Japanese	124/110
		IVS12-10A/G	Yes	Japanese	124/110
		IVS13-50G/A	Yes	Japanese	124/110
		IVS14119G/A	Yes	Japanese	124/110
ST2	11p14.3-p12	A-27639G	No	Japanese	452/636
STAT6	12q13	STR at exon 1	No	Chinese	94/186
TAP1	6p21.3	TAP1*A	No	Korean	53/184
TAP2	6p21.3	TAP2*A	Haplotype	Korean	53/184
TARC (CCL17)	16q13	C-431T	No	Japanese	193/158
		C2134T	No	Japanese	148/158
TIM1	12q12-q13	5383_5397del	Yes	Korean	112/201
TNFA	6p21.3	G-238A	No	Chinese	94/186
		G-308A	No	Chinese	94/186
		C-857 T	No	Chinese	94/186
		C-863A	No	Chinese	94/186
		T-1031C	No	Chinese	94/186

REFFERENCES

1. Desai N, Alexis AF. Atopic dermatitis and other eczema. In: Kelly AP, Taylor SC. Editors. Dermatology for skin of color. New York: McGraw-Hill Companies; 2009. p. 163–6.
2. Joyce TEL, Yuin CC. Common skin diseases and treatment in Asia. In: Kelly AP, Taylor SC. Editors. Dermatology for skin of color. New York: McGraw-Hill Companies; 2009. p. 611–26.
3. Meyers DA. Genetics of asthma and allergy: What have we learned? *J Allergy Clin Immunol* 2010; 126(3): 439–46.
4. Primavera G, Berardezka E. Biophysical properties of ethnic skin. In: Berardesca E, Leveque JL, Maibach HI. Editors. Ethnic skin and hair. New York: Informa Health Care; 2007. p. 13–8.
5. Stevenson A, Lindberg CA. New Oxford American Dictionary. 3rd ed. New York: Publisher Oxford Univ Press; 2010.
6. Corcuff P, Lotte C, Rougier A, Maibach H. Racial differences in corneocytes. *Acta Derm Venereol* (Stockh) 1991; 71: 146–8.
7. Sugino K, Imokawa G, Maibach H. Ethnic difference of stratum corneumlipid in relation to stratum corneum function. *J Invest Dermatol* 1993; 100: 597.
8. Meguro S, Arai Y, Masukawa Y, Uie K, Tokimitsu I. Relationship betweencovalently bound ceramides and transepidermal water loss (TEWL). *Arch Dermatol Res* 2000; 292(9): 463–8.
9. Kompaore F, Tsuruta H. In vivo differences between Asian, black and white inthe stratum corneum barrier function. Int Arch Occup Environ Health 1993; 65(suppl 1): S223–5.
10. Kompaore F, Marty JP, Dupont CH. In vivo evaluation of the stratum corneumbarrier function in Blacks, Caucasians and Asians with two noninvasivemethods. Skin Pharmacol 1993; 6: 200–7.
11. Wilson D, Berardesca E, Maibach HI. In vitro transepidermal water loss: differencesbetween black and white human skin. *Brit J Dermatol* 1988; 199: 647–52.
12. Berardesca E, Maibach HI. Racial differences in sodium lauryl sulphate inducedcutaneous irritation: black and white. Contact Dermatitis 1988; 18: 136–40.
13. Yosipovitch G, Theng CTS. Asian skin: Its Architecture, Function, and Differencesfrom Caucasian Skin. Cosmet Toiletr 2002; 117(9): 57–62.
14. Reed JT, Ghadially R, Elias PM. Effect of race, gender and skin type on epidermalpermeability barrier function. *J Invest Dermatol* 1994; 102: 537.
15. Berardesca E, de Rigal J, Leveque JL, Maibach HI. In vivo biophysical characterizationof skin physiological differences in races. *Dermatologica* 1991; 182: 89–93.
16. Rietschel RL. A method to evaluate skin moisturizers in vivo. *J Invest Dermatol*1978; 70: 152–5.
17. The International Study of Asthma andAllergies in Childhood (ISAAC) SteeringCommittee. Worldwide variation inprevalence of symptoms of asthma, allergicrhinoconjunctivitis, and atopiceczema. *Lancet* 1998; 351: 1225–32.
18. Williams HC, Pembroke AC, Forsdyke H, et al. London-born black Caribbean childrenare at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; 32: 212–7.
19. Mar A, Tam M, Jolley D, Marks R. Thecumulative incidence of atopic dermatitisin the first 12 months among Chinese,Vietnamese, and Caucasian infants bornin Melbourne, Australia. *J Am Acad Dermatol* 1999; 40: 597–602.
20. Diepgen TL. Atopic dermatitis: The roleof environmental and social factors, theEuropean experience. *J Am AcadDermatol* 2001; 45: S44–8.

21. Schultz Larsen F, Diepgen T, Svensson A.The occurrence of atopic dermatitis innorth Europe: An international questionnaire study. *J Am Acad Dermatol*1996; 34: 760–4.
22. Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitisin Oregon schoolchildren. *J Am Acad Dermatol* 2000; 43: 649–55.
23. Sugiura H, Umemoto N, Deguchi H, etal. Prevalence of childhood and adolescentatopic dermatitis in a Japanese population:Comparison with the diseasefrequency examined 20 years ago. *Acta Derm Venereol* 1998; 78: 293–4.
24. Nnoruka EN. Current epidemiology ofatopic dermatitis in southeastern Nigeria. *Int J Dermatol* 2004; 43: 739–44.
25. Worth R. Atopic dermatitis amongChinese infants in Honolulu and SanFrancisco. *Hawaii Med J* 1962; 22: 31–4.
26. Neame RL, Kurinczuk JJ, Graham-BrownRAC. Prevalence of atopic dermatitis inLeicester: A study of methodology andexamination of possible ethnic variation. *Br J Dermatol* 1995; 132: 772–7.
27. Baker RB. Incidence of atopic dermatitis and eczema by ethnic group seen within a general pediatric practice. *The Permanente Journal/ Winter* 1999; 3(1): 31–2.
28. Moore MM, Shiman SLR, Edwards JWR, Kleinman KP, Camargo CA, Gold DR, et al. Perinatal predictors of atopic dermatitis occuring in the first six months of life. *PEDIATRICS* 2004; 113(3): 468–74.
29. Brown SJ, McLean WHI. Eczema genetics: current stateof knowledge and future goals. *J Invest Dermatol* 2009; 129: 543–52.
30. Barnes KC. An update of the genetics of atopic dermatitis: Scratching the surface in 2009. *J Allergy ClinImmunol* 2010; 125: 16–29.
31. Akey JM, Eberle MA, Rieder MJ,Carlson CS, Shriver MD, Nickerson DAet al. Population history and naturalselection shape patterns of genetic variationin 132 genes. *PLoSBiol* 2004; 2: e286.
32. Baldini M, Lohman IC, Halonen M,Erickson RP, Holt PG, Martinez FD. Apolymorphism in the 5_ flanking regionof the CD14 gene is associated withcirculating soluble CD14 levels and withtotal serum immunoglobulin E. *Am JRespir Cell Mol Biol* 1999; 20: 976–83.
33. Zhang G, Goldblatt J, LeSouef PN. Does the relationship between IgE and the CD14 gene depend on ethnicity? *Allergy* 2008; 63: 1411–7.
34. Hoffjan S, Stemmler S. On the role of the epidermal differentiation complex in ichthyosisvulgaris, atopic dermatitis and psoriasis. *Br J Dermatol* 2007; 157: 441–9.
35. O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2008; 122: 689–93.
36. McKinley-Grant LJ, Idler WW, Bernstein IA, Parry DA, Cannizzaro L, Croce CM,et al. Characterization of a cDNA clone encoding human filaggrin and localizationof the gene to chromosome region 1q21. *Proc NatlAcadSci USA*1989; 86: 4848–52.
37. Gan SQ, McBride OW, IdlerWW, Markova N, Steinert PM. Organization, structure, and polymorphisms of the human profilaggrin gene. *Biochemistry* 1990; 29: 9432–40.
38. Sandilands A, Terron-Kwiatkowski A, Hull PR, O'Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncoversprevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007; 39: 650–4.
39. Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robustrisk factors in atopic disease. *J Allergy ClinImmunol* 2009; 123: 1361–70, e7.
40. Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F et al. Linkage and association of an interleukin4 gene polymorphism with atopic dermatitis inJapanese families. *J Med Genet* 1998; 35: 502–4.
41. Liu X, Nickel R, Beyer K, Wahn U, Ehrlich E, Freidhoff LR et al. An IL13 codingregion variant is associated with a high total serum IgE level and atopic dermatitis in the German multicenter atopy study (MAS-90). *J Allergy Clin Immunol* 2000; 106: 167–70.
42. He JQ, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J et al. Genetic variants of the IL13 and IL4 genesand atopic diseases in at-risk children. *Genes Immun* 2000; 34: 385–9.
43. Mao XQ, Shirakawa T, Yoshikawa T, Yoshikawa K, Kawai M, Sasaki S et al. Associationbetween genetic variants of mast-cellchymase and eczema. *Lancet* 1996; 348: 581–3.
44. Barker JN, Palmer CN, Zhao Y, Liao H, Hull PR, Lee SP et al. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol* 2007; 127: 564–7.
45. Weidinger S, Rodriguez E, Stahl C, Wagenpfeil S, Klopp N, Illig T et al. Filaggrinmutations strongly predispose to early-onsetand extrinsic atopic dermatitis. *J Invest Dermatol* 2007; 127: 724–6.
46. Brown SJ, Sandilands A, Zhao Y, Liao H, Relton CL, Meggitt SJ et al. Prevalent andlow-frequency null mutations in the filaggringene are associated with early-onset andpersistent atopic eczema. *J Invest Dermatol* 2008c; 128: 1591–4.
47. Shuk MH. Environmental epigenetics of asthma: An update. *J Allergy Clin Immunol* 2010; 126: 453–65.
48. Nakamura T, Sekigawa I, Ogasawara H, Mitshuishi K, Hira K, Ikeda S, Ogawa H. Expression of DNMT-1 in patients with atopic dermatitis. *Arch Dermatol Res* 2006; 298: 253–6.
49. Kuwubara N, Kondo N, Fukutomi O, Fujii H, Orii T. Methylation pattern of I epsilon region in B cells stimulated with Interleukin 4 and Epstein Barr virus inpatients with a high level of serum IgE. *Eur J Immunogonet* 1995; 22: 265–75.
50. Lorenzo PR, Kuwabara N, Kondo N, Orii T. IgE production by B cells stimulated with inteleukin 4 and Epstein Barr virus in patients with elevated serum IgE level. *J Invest Allergol Clin Immunol* 1995; 5: 78–81.
51. Strickland FM, Richardson BC. Epigenetics in human autoimmunity. *Autoimmunity* 2008; 41(4): 278