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Role of genetic aspect in pathogenesis of atopic dermatitis

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ABSTRACT

The pathogenesis of atopic dermatitis (AD) is a very complicated process that involves an intricate array of molecules. Nowadays it is generally accepted that cytokines play an important role in the progression of the clinical presentation of atopic dermatitis. However, emerging data point to the possible involvement of cornified envelope proteins in the development of skin barrier dysfunction and illness. Unfortunately, our knowledge on relation of particular genotype to progression of AD is very limited. Therefore, intensive studies are needed to increase our understanding of genetic background of atopic dermatitis. Hopefully the future research will identify new factors that help us to determine the additional risk for certain patients with atopic dermatitis.

KEY WORDS: allergic disease, SNPs, eczema, cornified envelope, interleukins

Introduction

Atopic dermatitis (AD, atopic eczema) is an inflammatory, chronic and recurrent dermatosis, whose dominant symptom is persistent and severe pruritus. Skin changes usually appear in early childhood, favoring typical locations and having a characteristic appearance (Leung & Bieber 2003). Living conditions and children maturation in the developed countries have fundamentally changed over the past years. The differences include frequency of infectious diseases, their treatment, contact with microorganisms, diet, chemical composition and pollution of air, all of which are connected with the constantly increasing incidence of allergies, especially in childhood and youth. The prevalence of atopic dermatitis has doubled or tripled in the industrialised countries over the past three decades; 15% to 30% of children and 2% to 10% of adults are currently affected by the illness (Williams & Flohr 2006). Atopic dermatitis is among the most frequently appearing skin diseases and is capable of coexisting with other IgE dependent atopic illnesses, e.g. with bronchial asthma, rash, allergic catarrh of the upper respiratory tract and nutritional allergy (Jansen *et al.* 1973). Type I (allergy) of hypersensitivity are the underlying reason for these illnesses. They represent a special kind of reaction of the organism. Sometimes a disproportionately small dose of antigen triggers dramatic manifestations (Custovic & Simpson 2012). The etiopathogenesis of AD is complex and still unexplained; immunologic, environmental and genetic factors are involved, and should be considered in the context of genes encoding structural and functional proteins of the epidermis and main elements of the immune system (Bieber 2008). The international HapMap project was started in 2002 to develop a public database that could help researchers find genes associated with human diseases and

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individual responses to pharmacological agents (http:hapmap.ncbi.nlm.nih.gov). Also, genome-wide association studies (GWAS) investigate the relationship between disease and common genetic variants spread across the genome (McCarthy *et al*. 2008). Meta-analyses have enabled researchers to distinguish loci of susceptibility to atopic dermatitis located on ten different chromosomes: 1, 2, 3, 5, 6, 7, 10, 11, 19, 20. In European populations, the loci 4q27, 5q31, 11p13, 11q13, 16p13.13, 17q21.32 and 19p13.2 were identified (Tamari *et al*. 2013; Ellinghaus *et al*. 2013). At present the attention of researchers is focused on seeking genes whose mutations or specific allelic forms predispose organisms to development of AD. Identification of genetic polymorphisms due to single nucleotide polymorphisms (SNPs) is the most common approach for finding genetic factors conditioning susceptibility to disease.

Genetic factors that influence development of the AD phenotype

Role of the skin barrier

Defects of the skin barrier, which physiologically constitutes the natural protection of the organism, are clearly associated with the disease phenotype (Boguniewicz & Leung 2011). The cornified envelope is the most important layer of epidermis due to the protection it from physical injuries and exogenous compounds. It consists of a number of dead, completely cornified cell layers. These cells are quite elastic, which helps them to fulfill their function. The cornified layer is hydrophobic thus, protects the skin against penetration of water from the environment and prevents dehydration of the organism (Alasdair *et al.* 1994). The cornified envelope consists of specialized proteins: loricrin (LOR), small proline-rich proteins (SPRR), a family of fused-type S100 proteins composed of filaggrin (FLG), repetin (RPTN), cornulin (CRNN), hornein (HRNR), and late cornified envelope-like proline-rich 1 (LELP1). Genes encoding these proteins are found within the epidermal differentiation complex (EDC), a gene cluster whose products are responsible for the final diversification of keratinocytes (Kypriotou *et al.* 2012). These proteins form a thick layer resistant to physical and chemical factors, influence production of natural moisturizing compound and ensure the appropriate pH of the skin, that prevents the penetration of infectious factors to its deeper layers. However, in AD patients, more rapid desquamation of the cornified layer occurs accompanied by exaggerated degradation of ceramides, which results in increased loss of water and increased permeability to exogenous allergens. This is frequently followed by the development of inflammation (Proksch *et al.* 2006). Moreover, reduced level of antimicrobial factors in the epidermis frequently results in recurrent bacterial infections in affected individuals (Bieber 2008). Therefore, genetic alterations including polymorphisms and mutations in genes encoding the proteins involved in the proper building of the epidermal barrier, may carry a certain degree of risk of the appearance of atopic dermatitis; this at present is being intensively studied.

Recent results of scientists from the University of Dundee provide a breakthrough in the area of AD genetics by revealing that *FLG* null alleles are a frequent transmissible predisposing factors in common atopic dermatitis. This study documented that inherited reduction or loss of filaggrin expression is a major predisposing factor in AD, and provided a molecular mechanism to define the coexistence of a clinical subtype of asthma (Palmer *et al*. 2006). These results initiated a flurry of research on this protein. Filaggrin functioning rely on binding of keratin fibers in the process of keratinocytes maturation. As a result of FLG conversion, a natural moisturizing factor is produced (Gan & McBride 1990). The metabolism of this protein result in an acidic pH generation in the cornified layer, an optimal environment for the enzymes synthesizing lipids of the cornified envelope (CE) (Markova *et al.* 1993).

R501X and 2282del4 are the most frequently occurring mutations of *FLG*. It was demonstrated that lack of FLG expression or its decrease in the skin caused by gene mutation occurs mainly in patients with early onset of the disease, a severe course of AD and elevated IgE levels (Palmer *et al*. 2006). It must be emphasized that *FLG* mutations occur only in a portion of AD patients. Moreover, in 9% of the European population, despite observed mutations, the atopic dermatitis phenotype was not developed. These results indicate the possible significance of polymorphisms and mutation within other than *FLG* genes encoding proteins of the epidermal differentiation complex (EDC) in the development of AD.

Loricrin is a major protein component of the cornified cell envelope found in terminally differentiated epidermal cells. It is a glycine-serine-cysteine-rich protein, synthesised in the granular (*stratum granulosum*) layer (Hohl *et al*. 1991). A connection between abnormal expression of *LOR* and skin diseases has been proven. Data has shown that mutation 730insG in *LOR*, which elongates loricrin by 22 amino acids due to delayed termination, is a factor in honeycomb palmoplantar keratoderma and the diffuse-ichthyosis form of dermatosis (Gedicke *et al.* 2005). Another study found that the down-regulation of loricrin and filaggrin was accompanied by up-regulation of some keratins in active AD skin lesions. The authors suggest that deterioration of epidermal differentiation associated with altered expression of genes located on 1q21 might be a key abnormality in atopic dermatitis (Weldinger *et al.* 2013).

The next gene to be identified as a possible factor in the development of AD is *LELP-1*. This gene encodes a late cornified envelope-like prolin-rich protein. Indian scientists found a significant link between rs7534334 SNP and log10 serum IgE levels in the group of patients (Sharma *et al*. 2007). However, this was only a single study and the authors stressed the need for further research.

A single nucleotide polymorphism within the gene encoding hornerin has recently been linked with susceptibility to atopic dermatitis (Henry *et al.* 2011). In the epidermis, hornerin was found to be co-localised with profilaggrin in keratohyalin granules in cells of the granular layer. These findings indicate that hornerin has a function similar to or mutually complementary to profilaggrin in the cornifying epithelium (Makino *et al.* 2001). Human protein hornerin was detected in regenerating skin following a wound and in psoriatic skin (Takaishi *et al.* 2012). It has been reported that allele C of rs877776 in *HRNR* gene is a risk factor of increased frequency of AD compared to controls even following exclusion of *FLG* mutation carriers (Esparza-Gordillo *et al.* 2009). In an Austrian population, single nucleotide polymorphisms, rs7927894 on chromosome 11q13.5 within the region of the *HRNR* gene, was identified as novel susceptibility variant for atopic dermatitis (Greisenegger *et al.* 2013). This study point to the statistically significant association of the rs7927894 variant with AD, but not with other disease-related phenotypes. Therefore, authors of that study postulated that the rs7927894 single nucleotide polymorphism selectively influences eczema development.

Repetin, a protein consisting of 784 amino acids, has a structure resembling the helix-calcium-binding-loop-helix domain of parvalbumin, hands of the S100 type and internal tandem repeats typical for CE precursor proteins (Huber *et al.* 2005). This protein associates with keratin intermediate filaments and is partially cross-linked to the cell envelope (Krieg *et al.* 1997). It has been proposed that this protein may be a marker of disturbances in differentiation of skin barrier cells and may be significant in the development of atopic dermatitis.

Polymorphism and mutations in the *CRNR* gene may also be associated with AD. Data has shown that human cornulin mRNA is expressed primarily in the upper layers of differentiated squamous tissues including the epidermis (Contzler *et al.* 2005). Data concerning eczema in Swedish families has shown that the *CRNN* polymorphism rs941934 is significantly associated with atopic eczema in the genetic analysis,

although only as part of an extended haplotype including a known associated variant 2282del4 in the filaggrin gene (Liedén *et al.* 2009).

The epidermal differentiation complex genes also encode the precursor protein of the cornified cell envelope, such as small proline-rich proteins (Hohl *et al.* 1995). The *SPRR* gene class consists of two *SPRR1* and seven *SPRR2* genes, along with a single *SPRR3* gene (Kartasova & van de Putte 1988). In human cornea tissue, the expression of SPRR1, SPRR2 and filaggrin protein were detected in the central and peripheral corneal and limbal epithelium (Tong *et al*. 2006). Cabral *et al.* noticed that the structural organization and regulation of the *SPRR* gene family reflects the epithelial barrier's role i.e. guarantee optimal protection to the organism (Cabral *et al.* 2001). Nomura *et al.* recently reported that SPRR2C, a component of the CE with a protective skin barrier function, showed the largest (eleven-fold) increase in psoriatic skin lesions as compared with AD (Nomura *et al.* 2003). Polish investigators noticed the deregulated increase in *SPRR* expression in chronic atopic skin lesions; *SPRR1A* and *SPRR2C* lose their coexpression with *S100* genes and other 1q21 transcripts (Jarzab *et al.* 2009). They hypothesize that this altered pattern reflects an insufficient rise in *SPRR* expression, which is unable to compensate for the lack of loricrin and thus contributes to the persistence of chronic AD skin changes.

The correlation of gene polymorphism with atopic disease was also observed. The data suggested a dominant mode of inheritance for the risk allele of *SPRR3* in eczema (Marenholz *et al.* 2011). In this study the frequency of appearance of the gene polymorphism rs28989168 among the AD patients and control group was analyzed. It appeared that the *SPRR3* variant associated with atopic dermatitis carried an extra 24-bp repeat in the central domain, which may alter the physical properties of the CE (Marenholz *et al.* 2011).

To sum up, among EDC genes several genes have been identified as factors contributing to the risk of AD development. This point the need of further research particularly since the present results have not been confirmed by independent laboratories and are mostly incomplete. More investigations involving distinct study populations are needed to assess the role of identified polymorphisms in atopic dermatitis. Identification of the genes that are deregulated in the atopic organism is thus likely to improve our understanding of AD pathogenesis [Tab.1].

Role of interleukins

Interleukins are molecules that regulate diverse processes, e.g. the proliferation, differentiation and mobility of cells. Acting on many cells, interleukins are mediators of inflammatory responses and immunologic processes. Also, keratinocytes, in response to barrier dysfunction, produce a variety of cytokines (Kayserova *et al.* 2012, Maeve *et al*. 2013). Therefore, investigators are also focused on examining genes encoding interleukins, which may play a role in development and progression of AD.

Interleukin 4 (IL-4) is produced through stimulation Th lymphocytes by an antigen. A correlation exists between IL-4 secretion and IgE concentration in plasma; its increased expression causes inflammatory responses of an allergic character (Namkung *et al*. 2011a). Czech investigators analyzed polymorphism in IL-4 receptor α (*IL-4Rα*) at position +1902 in patients with AD and a control group. This work showed a significant association between the genotypes of IL-4Rα and an increased level of tree-pollen-specific IgE (Kayserova *et al.* 2012).

The initial finding that interleukin-7 (IL-7) is produced by human keratinocytes suggested its possible involvement in skin diseases. A polymorphism T244I of receptor IL-7R was also found to increase the risk of AD in a group of German patients (Hoffjan *et al*. 2010).

Interleukin 9 (IL-9) is produced by stimulated T-lymphocytes, particulary Th2. This cytokine plays an important role in the regulation of antiparasitic response. It has

been suggests that SNP rs31563, located within the *IL-9* gene, is associated with increased susceptibility to AD (Namkung *et al*. 2011b). Similarly, rs3093467 SNP in the IL-*9R* gene seems to be associated with an increased risk of developing non-allergic AD (Namkung *et al*. 2011b).

Interleukin 12 and 13 (IL-12 and IL-13) are other cytokines that may play a critical role in AD. IL-12 is produced by antigen-presenting cells. It can also be secreted by keratinocytes (Namkung *et al*. 2010). IL-13 is similar in its action to IL-4, and receptors for these two cytokines share a common subunit (Hussein *et al*. 2011). Single nucleotide polymorphisms in IL-4 and IL-13 have been reported in patients with allergic diseases. Korean researchers noticed that two SNPs, rs3091307 and rs20541, from the *IL-13* gene showed a significant difference in allelic or genotypic distributions between AD and normal groups. However, they did not observe any associations for the *IL-4Rα* polymorphism C3223T or the *IL-4* polymorphism C590T (Namkung *et al*. 2011a).

TABLE 1. Genes with polymorphism and mutation linked to AD risk.

protein	**gene**	**SNP/mutation**	**Allel 1**	**Allel 2**	**Chromosome loci**	**Functional group**
Interleukin 9	*IL-9*	rs31563	C	T	5:135235606	cytokine-related
Interleukin 7 receptor alpha chain	*IL-7R*	rs11567705	C	G	5:35861152	cytokine - related
Interleukin 13	*IL-13*	rs3091307	A	G	5:131989136	cytokine - related
Interleukin 13	*IL-13*	rs20541	A	G	5:131995964	cytokine - related
Interleukin 18	*IL-18*	rs360721	C	G	11:112025916	cytokine - related
Filaggrin	*FLG*	R501X	C	T	1:152285861	skin barrier
Hornerin	*HRNR*	rs877776	C	G	1:152178018	skin barrier
Cornulin	*CRNR*	rs941934	C	T	1:152390452	skin barrier
Late cornified envelope-like proline-rich 1	*LELP-1*	rs7534334	C	T	1:153177852	skin barrier

Interleukin 10 (IL-10) fulfils many functions which result in suppression of immune response on a cellular level and inflammatory response (Lacy *et al*. 2009). Examinations conducted among children under the age of 3 years have shown the

potential role of *IL10* SNPs in the development of immune-mediated diseases, such as AD (Raedler *et al*. 2013).
Keratinocytes and epithelial cells can secrete interleukin 18 (IL-18). Genome – wide association study suggested IL-18R1 role for interleukins signaling (Hirota *et al*. 2012). Ibrahim *et al*. noticed that the -140 GG genotype and the -140 G allele were more often observed in patients with severe AD compared with mild and moderate phenotypes (Ibrahim *et al*. 2012).
Interleukin 31 (IL-31), produced by Th2 lymphocytes, acts on macrophages and keratinocytes. In these cells there is a receptor for this cytokine (Kasraie *et al*. 2013). It is postulated that IL-31 plays a role in AD pathogenesis. Associations between *IL-31* gene variants and eczema have previously been demonstrated in three independent European populations (Schulz *et al*. 2007).
The data accumulated to day indicate that the level of expression of genes encoding interleukins has a critical influence on the developing atopic dermatitis. Interleukins SNPs status of the organism can have great meaning if we want predict risk of allergy [Tab.1].

Conclusion

Atopic dermatitis is a multifactorial-disease. The data we presently have at our disposal show that there is no simple correlation associated with a single gene defect or with the occurrence of its determined allelic form and the risk of contracting the disease. It seems that the interaction of many genes plays a role in the progression of the disease. Moreover their expression is influenced by environmental factors. All authors emphasize the need to conduct intensive research to clarify the genetic basis of AD.

Determination whether a link exists between the frequency of appearance of the particular variant of the polymorphic gene coding protein s forming the cornified envelope or specific interleukins, on one hand, and the risk of atopic dermatitis on the other, will help us to better understand the pathogenesis of this disorder. This will influence the direction of research on new therapeutic methods and enable the development of a more effective and safer treatment for atopic dermatitis.

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