

Development of Atopic Dermatitis: Genetics or Epigenetics

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The prevalence of atopic dermatitis (AD) is generally reported to be around 20% in children, but the prevalence has been reported differently around the world. Most of this disease occur before the age of 2 years, and eczema become less common with increasing age. Atopic march is a term that describes the progression of atopic disorders, from eczema in young infants and toddlers to allergic rhinitis and finally to asthma in older toddlers and children. AD is often the first manifestation of atopic march. So understanding the process leading from it to respiratory comorbidities is an important part of understanding the natural course of it.

The various prevalence according to race suggests that its development is greatly influenced not only by the environmental factor, but also by genetic factors. A number of familial studies and twin studies have demonstrated that atopic dermatitis is a highly heritable disease. However, recent rapid increase of prevalence is not explained by genetics alone, suggesting that rapidly changing life style and environmental factors play a great role to this development. In this section, we discuss the genetics and epigenetics factors among many factors that affect atopic dermatitis development.

Basic concept of genetic study in allergic disease

AD is not a single genetic problem, such as cystic fibrosis, but complex genetic disorder. Familial aggregation of complex genetic disorder like this disease is proven when the risk of the disease is significantly higher among family members than whole population. Many studies have reported on familial aggregation of allergic disease. There are two general approaches in genetic study for allergic diseases. First one is the candidate gene association study, which is performed in disease groups and control groups, and second one is a hypothesis-independent approach,

that involves genetic variation studies on whole genes. The candidate gene association study evaluates genetic variation in the region of genes that are physiologically suggested to be involved in disease pathogenesis. It can include genes encoding cytokines, chemokines, and their receptors and those encoding transcription factors and the IgE receptor. The advantage of this study is that candidate genes have biological relevance and can often reveal functional outcomes that have potential implications for the disease of interest. The disadvantages of this study is that the discovery of new genes is restricted to genes that are supposed to be involved. The genetic variants typically used to conduct association studies are single nucleotide polymorphisms, which is called abbreviated as SNPs. The polymorphism of individual DNA sequences may be due to single nucleotide polymorphism or variations long DNA from several base pairs to thousands bases pairs. Among them, SNPs are the most common type of polymorphism and Human genome contains an estimated 10 million SNPs.

Genome-wide association studies in allergic disease

Genome-wide association studies (GWAS) has recently come to the forefront. Due to the mapping of polymorphisms in the genome and the advances in genotyping technology, it is possible to scan the whole genome of cases and controls in a hypothesis-independent manner to identify multiple susceptibility genes, each of which contributes a small effect. Microarray chips are available for genotyping 500,000 to 2,500,000 SNPs per person. The cost has progressively decreased, and the accuracy rates have increased, making this a powerful approach for studying the genetics of allergic diseases.

Genetic studies in atopic dermatitis

After June 2009, traditional genetic linkage studies for AD had been substituted by GWAS studies with large scale sample sizes in different populations. There were several GWAS studies on AD, and they include lots of subjects in discovery cohort and the replication cohort. In 2015, GWAS study for AD was performed Joint effort of multiple countries cross continents. This study included populations of European, African, Japanese and Latino ancestry. In this study, the new loci include candidate genes with roles in the regulation of innate host defenses and T cell function, underscoring the important contribution of immune mechanisms to AD pathogenesis.

A number of studies have recently investigated genes associated with skin barrier function. This is triggered by the identification of filaggrin gene (FLG), it plays an important role in skin barrier function. Filaggrin, which is a

filament-aggregating protein, is a major component of the protein-lipid cornified envelope of the epidermis, which is important for water permeability and for blocking the entry of microbes and allergens. FLG gene has a key role in epidermal barrier function and is one of the strongest genetic risk factors for atopic dermatitis. This is located on chromosome 1q21 in the epidermal differentiation complex. In 2006, it was recognized that loss-of-function mutations in *FLG* caused ichthyosis vulgaris and a predisposition to atopic dermatitis and associated asthma. Several studies in Korea also have reported that the FLG gene is associated with atopic dermatitis susceptibility. In GWAS studies, in Korean, five new candidate genes such as PCDH9, NBAS, THEMIS, GATA3, and SCAPER were identified in children with atopic dermatitis.

Epigenetic studies in atopic dermatitis

Epigenetics is biochemical changes to DNA that do not alter the DNA sequence but may be induced by environmental factors and transmitted through generations. Epigenetic factors include DNA methylation and modification of histones by acetylation and methylation. Modification of histones, around which DNA is coiled, alters the rate of transcription and alters protein expression. DNA methylation, which involves adding a methyl group to specific cytosine bases in DNA, can suppresses gene expression. Histone changes and DNA methylation can result from environmental exposures such as tobacco smoke and alterations in early-life environment such as maternal nutrition.

Conclusions

In conclusions, the field of genetics has developed remarkably, because of the development of bioinformatics, analytical techniques and transcriptional physiology. But, further studies are needed to understand the genetic factors of atopic dermatitis and to clarify the pathogenesis and treatment response. In the near future we will be able to analyze the genetic list of patients with atopic dermatitis and provide individualized and targeted therapy.

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