What is New and Hot in Genetics of Human Atopic Dermatitis: Shifting Paradigms in the Landscape of Allergic Skin Diseases

The immunologic abnormalities in patients with allergic skin diseases occur as a consequence of primary defects residing within the epidermis, suggesting an association between skin barrier dysfunction and immune abnormalities (1). The skin barrier is located in the uppermost layers of the epidermis, the stratum corneum, with important elements: intracellular keratin filaments, intercellular lipids, and a cornified cell envelope. It plays a vital role in all terrestrial forms of life, due to prevention of fluid loss and protection from microbial and allergen invasion. Functional lack of epidermal enzymes and structural skin proteins compromises skin barrier integrity and function. These deficiencies can even induce local changes in the expression of various inflammatory mediators, suggesting the direct immunologic role of the epidermis in the pathogenesis of allergic skin diseases (1). Primary isolated epidermal defects can result in allergy. Filaggrin (FLG), involucrin, and loricrin are among the most important structural proteins. Also, lipids play very important role, as well as some enzymes, such as serine proteases. Netherton syndrome is classic example of autosomal recessive disorder due to loss-of-function mutations in SPINK5, the gene encoding the SP inhibitor lymphoepithelial Kazal-type trypsin inhibitor (LEKTI) (2). Most importantly, mutations of filaggrin (FLG) gene, an essential component of the skin barrier, are associated with ichthyosis vulgaris and atopic dermatitis (AD). AD is inflammatory skin disease caused by inherited skin barrier deficiency, with mutations in FLG predisposing to development of AD. AD has highly heritable complex trait; however, environmental influences also play a role in triggering the atopic diathesis (3,4). Genome-wide association studies in AD have identified several susceptibility loci; however, the major and only functionally characterized genetic factor is FLG, which encodes skin barrier protein FLG (4). FLG is one of the most prominent genes responsible for barrier defect. FLG has been identified as a major locus causing skin barrier deficiency; however, not all patients with AD have this mutation, so AD cannot be explained by FLG mutation (3,4). Support for barrier deficiency initiating AD came from flaky tail mice, which have frameshift mutation in FLG and also carry an unknown gene, the Matt gene, causing a matted hair phenotype (1,4,5). This phenotype in flaky tail mice is due to a mutation in the Tmem79/Matt gene, with no expression of the encoded protein mattrin in the skin of mutant mice. Sasaki *et al.* and Saunders *et al.* report successful delineation of the genetic basis of the flaky tail mouse phenotype (1,4,5). Flaky tail mice display a matted hair phenotype and have spontaneous dermatitis under pathogen-free conditions; and have been used over the years as a model for AD (1). These mice arose spontaneously as the result of crosses between mice carrying a recessive mutation named *matted* (ma), and have been since maintained as double mutants (maft) (1). It has recently been found that flaky tail mice carry a deletion in the mouse FLG gene, suggesting that FLG deficiency might explain their propensity to have dermatitis, analogous with the situation in some human patients with AD (not all patients with AD have FLG mutation). Genetically engineered FLG-deficient mice display impaired barrier function, but lack the propensity of spontaneous skin inflammation of flaky tail mice. Matted mice spontaneously develop dermatitis and atopy caused by a defective skin barrier, with mutant mice having systemic sensitization after cutaneous challenge with house dust mite allergens. The matted phenotype was found to be due to a loss-of-function mutation in Tmem79 (4,5). Unexpectedly, the Tmem79 mutation, rather than the deletion in FLG, was found to be associated with the development of dermatitis in mice (1). Moreover, exogenous Tmem79 expression

was able to rescue both the hair and the dermatitis phenotype in flaky tail mice (1). These studies have elucidated the relative contributions of the FLG and Matt mutations in DM mice (1). These data indicate that the DM mouse is not a true model of FLG deficiency-associated AD-like skin (3). Tmem79 is mainly expressed in the granular layers of the epidermis, where its absence correlates with abnormal function of lamellar granules (1,5). Those lamellar granules are Golgi-derived specialized organelles, responsible for transferring lipids and proteases to the upper part of the epidermis (5). Therefore, Mattrin could be a link between protein and lipid interaction in etiopathology of AD. Meta-analysis of 4.245 AD cases and 10.558 population-matched control patients showed that a missense SNP, rs6694514, in the human Matt gene has a small but significant association with AD (3). Expression quantitative trait locus analysis showed that Matt is in a network of proteins expressed late in epidermal differentiation, with an expression quantitative trait locus profile closely matching that of Rhbg (transporter protein) and Rab25 (membrane trafficking) (4). Mattrin shows distant sequence homology to the membrane- associated proteins in eicosanoid and glutathione metabolism (MAPEG) protein family (4). Matt mutation results in defective expression of the transmembrane protein mattrin, which is highly expressed in the upper granular layer of epidermal keratinocytes, with a predicted role in lipid homeostasis. It is interesting to mention that authors noted that FLG mutation has a neonatal influence, whereas Matt mutation shows progressive influence with age. This indicates the polygenic nature of the DM mouse as an AD model and indicates the differential influence of both the FLG and Matt mutations (4).

Recently, four new susceptibility loci for AD were identified and previous associations were replicated, which brings the number of AD-risk loci reported in individuals of European ancestry to 11 (7). It is estimated that together, these susceptibility loci account for 14.4% of the heritability for AD (7). Genome-wide association studies (GWAS) have shown remarkable overlap across immune-mediated diseases (7). Two European GWAS on AD established four susceptibility loci (C11orf30, OVOL1, ACTL9 and RAD50-IL13-KIF3A) in addition to *FLG* (4-6). At C11orf30, the same allele also confers risk to asthma and Crohn's disease (5,9-11). For RAD50-IL13, locus agonistic effects were observed for asthma, and locus antagonistic effects were observed for psoriasis (6,12,13). Two further loci were reported in a Chinese GWAS (TNFRSF6B-ZGPAT and TMEM232-SLC25A46) (14). All loci were confirmed in a recent Japanese GWAS, which additionally reported eight new loci (IL1RL1-IL18R1-IL18RAP, MHC, OR10A3-NLRP10, GLB1, CCDC80, CARD11, ZNF365, and CYP24A1-PFDN4) (15). However, the causal variants at all loci except FLG are unknown (6).

In conclusion, we can state that FLG has been, and still remains the major susceptibility gene in patients with AD, but genetic pathways in atopic patients are complex and influenced by the environment, including multiple genes involved in skin barrier, as well as proteins, lipids, and enyzmes interacting with immune system. Therefore, we have many future lessons to learn from the genetics of atopic diseases.

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