

EDITORIAL

Genetics of Atopic Dermatitis

Beyond Filaggrin—the Role of Thymic Stromal Lymphopoietin in Disease Persistence

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In this issue of *JAMA Dermatology*, Margolis et al¹ report the association of a thymic stromal lymphopoietin (*TSLP*) variant with disease remission in children with atopic dermatitis (AD), particularly in those carrying filaggrin gene (*FLG*) mutations. Thymic stromal lymphopoietin, an epithelial cell-derived cytokine, is a master initiator of helper T cell type 2 (T_H2) differentiation and allergic manifestations.² These results suggest that *TSLP* could be a possible dual factor in AD, capable of modulating the effects of *FLG* mutations in triggering allergic manifestations. Alternatively, this single-nucleotide polymorphism (SNP) variant could be in linkage disequilibrium, with a causative variant to be identified, localized within or outside *TSLP*. Functional and expression studies of this *TSLP* SNP variant will be instrumental to assess its role(s) in the disease.



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Atopic dermatitis is a relapsing chronic inflammatory skin disease characterized by eczematous skin lesions and intense pruritus³ and is the most common inflammatory skin disorder, with an increasing prevalence. It affects up to 20% of children and 3% of adults in developed countries. Atopic dermatitis is an allergic disorder, often associated with asthma or other allergic manifestations. The cutaneous manifestations of atopy often represent the beginning of the atopic march. There is considerable clinical heterogeneity of the disease with regard to the age of onset, clinical manifestations, severity, and associated allergic manifestations and complications, suggesting etiological heterogeneity. Atopic dermatitis currently lacks specific effective treatment, although the use of calcineurin inhibitors has significantly brought a clinical benefit to patients.

Atopic dermatitis is a multifactorial disease caused by complex interactions between multiple genetic determinants and environmental factors. A major breakthrough in the understanding of AD pathogenesis was the identification of mutations in *FLG*.⁴ Loss-of-function mutations in *FLG*, encoding a key protein involved in maintaining skin barrier function, have been consistently, widely, and strongly associated with AD, demonstrating the important role of epidermal barrier defects in AD. To date, 4 recurrent *FLG* mutations (R501X, 2282del4, S3247X, and R2447X), with an estimated combined allele frequency of approximately 7% to 10%, and several less common variants have been identified in individuals of European descent. Notably, the same *FLG* mutations identified in the European population were rarely found in Asians

or Africans.⁴ The prevalence of *FLG* mutations is similar in Europeans and Asians. In contrast, *FLG* mutations seem to be less common in African populations, although they have been less extensively studied, with the consequent possibility of underestimating the frequency of distinct *FLG* mutations. The strongest associations have been reported between *FLG* mutations and the risk of early-onset, persistent, and severe AD.⁴ The striking implication of *FLG* mutations as a major genetic predisposing factor for AD has placed a new focus on the role of barrier impairment in AD pathogenesis. The pathogenesis of AD therefore implicates structural abnormalities in the epidermis as well as immune system.³ The epidermal barrier disruption contributes to impaired protection against environmental irritants and allergens. This results in the activation of antigen-presenting cells, leading to sensitization and the development of a T_H2 response underlying allergic manifestations. Several studies have revealed the key roles of dendritic cells signaling T_H2 polarization, specific IgE production, and mast cell and eosinophil activation in AD.³

In support of the role of *TSLP* in allergy, *TSLP* level is increased in the skin of human patients with AD and is known to induce T_H2 differentiation, and several studies have reported significant or suggestive evidence of an association of *TSLP* SNPs with multiple allergic disorders.⁵ One study investigated the association between *TSLP* tag SNPs and the risk of AD or a rare and serious complication of AD, eczema herpeticum (ADEH).⁶ Suggestive evidence of an association with AD was reported for 3 *TSLP* SNPs in both European and African American populations, although for different sets of SNPs. Rs1898671 and rs2416259 variants were associated respectively with lower and increased risk of ADEH among European Americans. Specifically, rs1898671 showed the strongest association, which remained significant after correction for multiple testing. Interestingly, the authors also reported that *FLG* mutations were more frequent in patients with ADEH than those without ADEH.

To date, 2 SNPs in the *TSLP* promoter were demonstrated or suggested to be functional.⁷ The minor allele of rs3806933 increases *TSLP* promoter activity and expression through enhanced AP-1 binding, whereas the minor allele of rs2289276 was suggested to enhance transcriptional activity by diminishing AP-2α binding. These alleles were associated with an increased risk of asthma. There is no functional data for other *TSLP* SNPs. Taken together, these findings pointed to *TSLP* as an important candidate for AD susceptibility and severity, particularly ADEH.

In addition to the well-established *FLG* locus on chromosomal region 1q21 with the epidermal differentiation complex (EDC), several genome-wide association studies and meta-analysis conducted in European or Asian populations have identified new susceptibility loci.⁸⁻¹⁰ Interestingly, the 5q22.1 and the 3p21.33 loci are located, respectively, adjacent to the *TSLP* and the *CCR4* genes, encoding a chemokine receptor for TARC (thymus- and activation-regulated chemokine), whose production by dendritic cells is induced by *TSLP*.⁸

Margolis et al¹ tested the association of several *TSLP* SNPs with AD severity and persistence and whether these SNPs modulated the effects of *FLG* loss-of-function mutations (R501X, 2282del4, S3247X, and R2447X). Briefly, they evaluated the association of 14 *TSLP* tag SNPs with the nonpersistence of AD symptoms over time in a multiyear prospective cohort study of white and African-American children, the Pediatric Eczema Elective Registry. The cohort includes patients with mild to moderate AD evaluated every 6 months. All participants received pimecrolimus treatment, a calcineurin inhibitor, before the start of the study. The phenotype studied was the absence of symptom for 6 months after discontinuation of topical medication. Margolis et al¹ demonstrate that rs1898671 is significantly associated with less persistent AD in white individuals, and the same trend was observed in African American subjects and the pooled population. Interestingly, the same SNP was also reported to be associated with a lower risk of ADEH among European Americans but not with AD outcome.⁶ Thus, 2 independent studies reported a protective effect of the same SNP on disease evolution (lower risk of ADEH or AD persistence).^{1,6} These findings suggest that this variant is associated with AD severity, evolution, or persistence rather than the risk of developing AD. Nevertheless, surprisingly and inconsistently, suggestive evidence of an association with an increased risk of other atopic manifestations, including asthma, allergic rhinitis, or eosinophilic esophagitis, was reported for this SNP in European populations.¹¹⁻¹³ No association with asthma risk was identified in the study by Margolis et al.¹ These conflicting results of the effect of rs1898671 on AD and other allergic manifestations need further confirmation and investigation. The second SNP, rs2416259, previously reported to be associated with an increased risk of ADEH, was not associated with persistence of AD in the current study by Margolis et al.¹

Previously, Margolis et al¹⁴ demonstrated that *FLG* mutations were associated with an increased persistence of AD in

the same cohort. In their current study,¹ the association reported between rs1898671 and AD remission is stronger in the subgroup of patients with *FLG* mutations. Thus, patients with *FLG* mutations and rs1898671 SNP had less persistent AD compared with those with *FLG* mutations only. These results suggest that rs1898671 acts in opposition to *FLG* mutations and partially reverse the deleterious effect of these mutations. This result supports the concept that skin barrier defect is the primary culprit of AD pathogenesis. Skin abnormalities enable enhanced penetration of environmental allergens into the skin, initiating immunological reactions and inflammation. Decreased immune system response may counter consequences of barrier dysfunction.

The 2 *TSLP* promoter SNPs (rs3806933 and rs2289276) showed no association with AD persistence in the study by Margolis et al.¹ The Encyclopedia of DNA Elements (ENCODE) project, which aims to identify all functional elements in the human genome, including marks of accessible chromatin and protein binding sites, provides a rich source of information to correlate association results with functional data. Based on ENCODE, there is little evidence that the intronic *TSLP* SNP, rs1898671 (score 5 from RegulomeDB variant classification [<http://www.regulomedb.org>]), may be a regulatory variant with functional consequences. Therefore, in the absence of evidence for a functional effect, this SNP is probably not causal, but rather a tag SNP in linkage disequilibrium with an unknown etiologic variant. This variant could lie within or outside *TSLP*, and refined association studies may help in investigating this possibility. In particular, rs1898671 is in high linkage disequilibrium ($r^2 > 0.8$) with SNPs in the *WDR36* gene, which is involved in T-cell activation. The findings by Margolis et al¹ suggest that rs1898671, or more likely a variant in linkage disequilibrium, may have a protective effect on AD, possibly through diminishing *TSLP* expression or protein activity. The investigation of the correlation between the associated SNP and *TSLP* expression, protein level, or activity in in vitro models and/or in patients with AD will be of great interest to test this hypothesis.

These genetic findings contribute to improve our understanding of AD pathogenesis. Their potential translation for the development of adapted treatment represents a considerable challenge for the future. Recently, a new therapeutic strategy based on up-regulating filaggrin expression has been proposed.¹⁵ Similarly, the prevention of *TSLP* overexpression is a promising target for the treatment of AD, especially in patients with altered barrier skin due to *FLG* mutations.⁵

ARTICLE INFORMATION

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