COMMENTARY

of life occur in achieving PASI 75, will insurers pay for expensive drugs just to get to PASI 90 or PASI 100, even if those levels of improvement have been associated with greater quality of life improvements?

And, are there other factors, such as environmental factors or phenotypic factors, that should be considered along with biomarkers to predict responders? For example, are obese patients more or less likely to respond? Trials with most drugs would suggest that low body weight improves the likelihood of response.

In an era of personalized medicine, the ability to identify genetic markers that predict response to medications is certainly valuable, but the value might be even greater for drugs that do not achieve such high response rates. Acitretin, methotrexate, and apremilast, for example, require months of treatment before achieving optimal benefit, and the proportion of PASI 75 responders in those three groups is less than 50%. A biomarker to predict response to any of those drugs would certainly be welcome.

As the treatment options for psoriasis increase, the availability of biomarkers would certainly be welcome, but we all hope to see the day when we have a completely safe medication that allows 100% of patients to achieve PASI 100. At that point, we will not need a genetic marker to predict response.

CONFLICT OF INTEREST
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In this elegant study, Manz et al. further our understanding of the pathogenesis of atopic dermatitis by demonstrating the functional importance of variations in LRRC32 on the well-established 11q13.5 atopic dermatitis risk locus.

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Atopic Dermatitis According to GARP: New Mechanistic Insights in Disease Pathogenesis

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In complex disease such as atopic dermatitis, the journey from identification of strong risk loci to profound functional and mechanistic insights can take several years. Here, Manz et al. have elegantly deciphered the mechanistic pathways in the well-established 11q13.5 atopic dermatitis risk locus. Their genetic and functional insights emphasize a role for T regulatory cells in atopic dermatitis pathogenesis.


The etiology of atopic dermatitis (AD) is multifactorial. It includes interactions between environmental and genetic factors that lead to skin barrier disruption and both cutaneous and systemic immunologic dysfunction (Weidinger and Novak, 2016). Although null mutations in FLG, encoding an epidermal barrier protein, are the strongest and best replicated genetic risk factors for AD, these mutations are present in only up to 50% of patients (Irvine et al., 2011), meaning that identification and deeper understanding of other genetic risks involved in this complex trait are required. To date, genome-wide association studies have identified more than 30 loci associated with AD risk (Paternoster et al., 2015). These loci include candidate genes harboring roles in innate and acquired immune responses, emphasizing the importance of immune responses in AD. Of these 31 loci, FLG on Chr1q21 is the only locus for which a significant body of functional and genotype/phenotype correlative data has been generated (McAleer and Irvine, 2013). One susceptibility region, on chromosome 11q13.5, was reported initially in 2009 (Esparza-Gordillo et al., 2009), and it has been replicated as an AD risk locus in several subsequent studies (O’Regan et al., 2010, Paternoster et al., 2015). It has also been associated with other allergic and inflammatory diseases (Barrett et al., 2008; Marenholz et al., 2015); however, the functional role of variants in this locus in AD pathogenesis was unknown. Manz et al. (2016) report genetic association and functional data that reveal an important role for glycoprotein A repetitions predominant (GARP) in the pathogenesis of AD.

Using a targeted next-generation sequencing of the 11q13.5 locus in
patients with AD, they identified six low allele frequency single-nucleotide variants in the coding sequence of the \textit{LRRC32} gene. They then studied the functional consequences of these variants and highlighted the role of T regulatory cells (Tregs) in AD pathogenesis. The \textit{LRRC32} gene encodes GARP, a transmembrane protein, consisting of an extracellular domain with 20 leucine-rich repeats, a leucine-rich C-terminal flanking domain, and a membrane spanning domain. GARP is a known cell surface receptor on activated Tregs, platelets, and certain cancer cells. The extracellular domain of GARP is a binding site for latent transforming growth factor-\(\beta\) (TGF-\(\beta\)), composed of latency-associated protein and active TGF-\(\beta\) that can be released through multiple mechanisms (Fridrich et al., 2016). Among \textit{LRRC32} variants found in the AD samples, five were located in the extracellular domain and one was located in the intracellular domain. The variant \textit{A407T/rs79525962}, located in the extracellular domain, was most frequent in German patients with AD, showing a significant association in more than 2,000 patients compared with 2,000 controls (Manz et al., 2016). Using in silico modeling, the authors predicted that their identified mutations would interfere with GARP post-translational modifications and/or protein folding, therefore affecting protein function and transport. Overexpression studies of the A407T variant in healthy donor T cells as well as analysis of T-cell subsets from patients carrying this variant showed a significant reduction of the mutated GARP protein on the cell surface (Manz et al., 2016). The authors suggested that this reduction in GARP surface expression may cause impaired interaction with circulating latent TGF-\(\beta\). Indeed, lower expression of latency-associated protein on Tregs converted from CD4\(^{+}\)CD25\(^{-}\) T cells on stimulation was observed in A407T AD carriers.

In recent years, several groups have reported a role for GARP in Treg function. Knockdown of GARP by using shRNA or blocking antibodies against GARP amino acids within GARP/TGF-\(\beta\) complexes reduced Treg suppressive activity (Fridrich et al., 2016). Tregs are known to play an important role in controlling responses of effector T cells, B cells, dendritic cells, eosinophils, and mast cells, thus preventing autoimmunity and allergic responses, moderating inflammation, and maintaining immune tolerance (Zhang et al., 2014). Numerous studies have shown the importance of Tregs in many inflammatory and autoimmune conditions, including asthma, multiple sclerosis, and type 1 diabetes (Ray et al., 2010). Although increasing interest has been devoted to the role of Tregs in AD, much remains to be learned. Recently, a murine AD model revealed an increase in the Treg population along with increased expression of surface markers, including GARP (Moosbrugger-Martinz et al., 2016). In the present research, there was a reduced conversion rate of CD4\(^{+}\)CD25\(^{-}\) T cells into Tregs obtained from A407T carrier AD patients compared with wild-type AD patients (Manz et al., 2016), addressing the role of the identified GARP mutation in Treg maintenance in AD patients.

In this elegant study, Manz et al. have added a new dimension to our understanding of the genetic architecture of AD. As is always the case with new discoveries, many new questions are generated. For example, do these mutations, which alter surface GARP expression, have any effect on the release of active TGF-\(\beta\) by Tregs and consequently on downstream TGF-\(\beta\)-driven immune dysfunction? Given that Tregs have the capacity to suppress immune reactions, including T helper type 2 responses to allergens, and that AD is often associated with allergic comorbidities, it will be of interest to study the association of identified variants in different subtypes of AD stratified by the development of sensitization and allergy. It will also be useful to determine whether these variants are relevant in other ethnicities or if there are additional ethno-specific mutations in other populations. Similarly, potential epistatic effects with other AD risk alleles, including \textit{FLG} loss-of-function mutations and other AD risk loci, will be worth exploring in larger cohorts or collections of patients. Identification of such genotype-phenotype associations may help in disease stratification and in planning individualized therapeutic approaches.

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