Allergy Asthma Immunol Res. 2021 May;13(3):360-362
https://doi.org/10.4168/aair.2021.13.3.360
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

How do Host Genetic Factors Affect Gut Microbiome in the Development of Atopic Dermatitis?

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▸ See the article "Interactions between IL-17 variants and *Streptococcus* in the gut contribute to the development of atopic dermatitis in infancy" in volume 13 on page 404.

Received: Jan 26, 2021
Accepted: Jan 27, 2021

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Disclosure
There are no financial or other issues that might lead to conflict of interest.

Atopic dermatitis (AD) is one of the most common chronic diseases in children.[1] Complex associations between genetic, environmental and immunological factors induce the development of AD.[1] The gut microbiome is considered our second genome and is linked to AD.[2] Not only environmental factors including diets and medications but also genetic factors can affect the shaping of gut microbiome.[2] Until now, associations between the development of AD and gut microbiome dysbiosis/genetic predisposition have been evaluated in parallel. For example, dysbiosis of *Faecalibacterium* in the human gut microbiome is associated with AD,[3] and interleukin (IL)-17 polymorphism predisposes to increased severity of AD.[4] However, there have been few studies on the co-association of complex host genetic factors and microbial compositions with childhood atopy.[5,6]

Meanwhile, a previous study has shown that perinatal exposure to environmental factors which affect shaping of the intestinal microflora interacts with IL-13 and CD14 polymorphisms to develop AD during infancy.[7] It has been suggested that environmental risk factors and genetic predisposition can additively affect the development of AD. However, there is limited data that showed effects of individual genetic variants on gut microbiome. Thus, further determination of the extent and nature of host genome-microbiome associations in AD is an important next step in understanding the exact pathogenetic mechanisms.

In the current issue of *Allergy, Asthma & Immunology Research*, Kang *et al.*[8] investigated how genetic variants affect the composition of the gut microbiota and the development of AD. They hypothesized that host genetic variants related to gut microbial taxa would be associated with AD development. To confirm the hypothesis, they performed genotyping in cord blood and metagenomic shotgun sequencing in fecal samples from 99 normal healthy and 61 AD infants at 6 months of age. They tested correlations between microbial composition and IL-17 variants known as AD risk loci[9] and identified a significant association between the A allele of IL-17 variants and increased relative abundance of *Streptococcus* in relation with AD. They found that increased *Streptococcus* and the A allele of IL-17 (rs2275913) contribute to the pathogenesis of AD via modulation of the immune system and showed that *Streptococcus*-enriched infants with AD were higher in those with the GA + AA of IL-17. These results are worth noting to explain the potential effect-modifying role of genetic variations in the relationship between the intestinal microbiota and AD development.

In this study of Kang *et al.*,[8] the authors examined gene variants of IL-17 which plays as a key cytokine in allergic inflammation as well as host defense against infection. They demonstrated that IL-17 expression was increased with gut inflammation and associated with Streptococcal colonization; thus, it is associated with the development and severity of AD. Previous studies have demonstrated the effect of genetic variants of IL-17 on the severity or development of AD.[4,9] For example, children with the A/A genotype in IL-17A have increased AD severity,[4] and IL-17-G152A entailed increased risk of developing AD.[9] However, these results did not show the complex association of IL-17 variants with the gut microbiome in the development of AD. In this regard, Kang *et al.*[8] demonstrated how the interactions between genetic factors (IL-17) and environment (gut microbiota) cooperatively result in AD.

The functional relevance of associations between IL-17 variants and specific species in the gut microflora is also crucial. To explore functional interactions between genotype and gut microbiome, the authors analyzed the concentrations of short-chain fatty acids and assessed mRNA expression levels of pro-inflammatory cytokines in human intestinal epithelial cell line after stimulation with IL-17 and/or *Streptococcus mitis* (*S. mitis*). It was demonstrated that the abundance of butyrate and valerate were distinct in infants with AD who had IL-17 variant and the mRNA expression of IL-6 and IL-8 by stimulation of a combination of IL-17 and *S. mitis* was greater than by either alone. They suggest that genetic variants in the IL-17 promoter are functionally associated with AD through modulation of the gut microbiome.

In this issue, Kang *et al.*[8] indicated the importance of understanding host-microbe interactions to gain better insights into AD. They showed significant differences in relative abundance of genes related to oxidative phosphorylation among the 4 groups. It suggests different functional profiles according to genetic variants and AD status. Identifying associations between human genetic variants and the gut microbiome, and exploring their interactions can provide a new insight into the role of the microbiome in AD, which points to interactions between host genetics and microbial dysbiosis as important contributors to AD. Together with evidence for different roles of the microbiota in AD,[10] their findings encourage further investigations into the interactions between genetic variants and the gut microbiome.

In conclusion, gene-microbiome interactions would be helpful in understanding enriched functional networks in immunity and gut inflammation, both of which play roles in the development of AD. However, since there are potentially millions of genetic polymorphisms and thousands of bacterial taxa and genes, a larger number of subjects and more genes are required to gain enough power of the host genome-microbiome association test.

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