

Gut Microbiota Influence Host Metabolism and Immune Responses in Atopic Dermatitis: A Next-Generation Sequencing-Based Functional Profiling Study

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Purpose: Gut dysbiosis has been linked to immune imbalance in allergic diseases, but the underlying mechanisms remain unclear. We aimed to verify whether gut microbiota composition is associated with cellular, metabolic, and immune pathways in atopic dermatitis.

Patients and Methods: Fifty adults with atopic dermatitis and 25 sex- and age-matched healthy controls were enrolled. Gut microbiome composition was assessed using V3–V4 16S rRNA sequencing. Functional pathways were inferred from microbiome data using PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States).

Results: Despite only subtle differences in microbiota composition between patients with atopic dermatitis and controls, PICRUSt analysis identified significant differences in 149 functional pathways. Key pathways enriched in atopic dermatitis involved signal transduction mediated by protein kinases, as well as carbohydrate and lipid metabolism. Downregulated pathways included those related to energy metabolism, amino acid and nucleotide metabolism, antigen processing, and innate immune responses. In patients with atopic dermatitis, microbial diversity increased with EASI scores and IgE levels, correlating with additional predicted functional shifts.

Conclusion: Our results suggest that even subtle structural differences in gut microbiota may exert significant functional effects in atopic dermatitis. Altered pathways could contribute to immune imbalance and impaired epidermal barrier function. These findings underscore the importance of incorporating functional analyses into future gut microbiota studies of atopic dermatitis to help identify therapeutic targets, including candidate probiotic strains for supplementation.

Plain Language Summary: Bacteria living in the gut, known as the gut microbiome, may play a role in the development of certain diseases. Changes in the diversity and composition of the gut microbiome have been linked to atopic dermatitis, a skin condition that causes itchy lesions and greatly affects quality of life. However, few studies have examined how gut bacteria may influence metabolism and immune responses in people with atopic dermatitis.

In our study, we analyzed the gut microbiome of 50 adults with atopic dermatitis and 25 healthy individuals using sequencing methods and a software tool called PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States). Despite only subtle differences of microbiome composition between the groups, PICRUSt predicted changes in many metabolic, cellular, and immune-related pathways. These included carbohydrate, lipid, and amino acid metabolism, innate immune responses, and signal transduction pathways that may contribute to inflammation and skin barrier problems seen in atopic dermatitis.

Our findings suggest that even when overall microbiome diversity appears similar, subtle changes in gut bacteria may still have important effects on metabolism and immune function. Future studies should combine microbiome and metabolic analyses to confirm these results and may help guide targeted treatments, such as probiotic supplementation.

Keywords: atopic dermatitis, gut microbiome, immunity, metabolism, microbiota

Introduction

Atopic dermatitis (AD) is one of the most common inflammatory skin disorders, marked by eczematous lesions in age-dependent distribution and distressing symptoms such as pruritus and insomnia.^{1,2} It is often associated with other atopic conditions, including allergic rhinitis, asthma, and food allergies. AD arises from a complex interplay of genetic predisposition and environmental factors.³ Most patients exhibit an epidermal barrier defect, which predisposes them to immune dysregulation and dysbiosis of the cutaneous microbiome. Type 2 inflammation is a hallmark of AD, though upregulation of molecular pathways mediated by Th17, Th22, and Th1 cells may also play a role.⁴

There is growing evidence suggesting the impact of structural changes of the gut microbiota on AD and other atopic disorders. A recent population-based study of school-aged children found that higher alpha diversity in the gut microbiota, along with an abundance of specific species (eg, *Lachnospiraceae*, *Ruminococcaceae*_UCG-005, and *Christensenellaceae*_R-7_group), was inversely associated with the risk of eczema.⁵ However, no functional pathways were linked to these outcomes. Simultaneously, a systematic review of prior observational studies concluded that findings regarding altered alpha- and beta-diversity in the gut microbiota of patients who later developed AD, compared to healthy individuals, were inconsistent.⁶ These discrepancies suggest that the gut microbiota's role in AD should be assessed not just by its composition but also through functional profiling.⁷ Notably, gut microbiota maturation in childhood is dynamic and influences immune and metabolic pathways. However, studies on its composition and functional impact in adults with AD remain limited.⁸ Importantly, although AD is most prevalent in children, adults often present with distinct clinical features, eg head-and-neck eczema and hand eczema, which may partly relate to differences in immune and metabolic pathways.⁹ Whether and how the gut microbiota contributes to these adult-specific patterns remains unclear and warrants further investigation.

Therefore, this study aimed to analyze the gut microbiota composition in adult patients with AD and healthy controls and to perform functional analyses to predict its impact on cellular, metabolic and immune pathways in these populations.

Methods

The research conformed to the principles of the World Medical Association's Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Medical University of Warsaw (approval no. KB/141/2020 with subsequent amendments). All participants provided written informed consent prior to enrollment in the study.

Study Participants

Patients with active AD, diagnosed according to the Hanifin and Rajka criteria were enrolled in the study. Individuals who were receiving systemic medications, probiotics, or supplements were excluded. Treatments such as antibiotics, immunosuppressants, and biologics were discontinued at least six months prior to participation in the study. The use of topical corticosteroids, calcineurin inhibitors, and emollients was permitted. All patients were examined by the same investigator (LB). Disease activity was assessed using the Eczema Area and Severity Index (EASI) score. A sex- and age-matched control group was also enrolled, following similar inclusion and exclusion criteria as the study group.

Total IgE serum concentration was measured in all participants using the enhanced electrochemiluminescence method, with readings performed on the Cobas c 501 Chemistry Analyzer (Roche Diagnostics, Rotkreuz, Switzerland). An elevated IgE serum concentration was defined as ≥ 100 IU/mL, while concentrations ≥ 1000 IU/mL were categorized as very high, based on previous studies.¹⁰ Stool samples were collected within 24 hours of the visit and immediately stored at -80°C for further analysis.

All study participants provided informed consent prior to enrollment. The research protocol was approved by the Institutional Review Board (approval no. KB/141/2020 with subsequent amendments).

DNA Extraction and Sequencing

DNA was extracted from 180–220 mg of stool using the Nucleospin DNA Stool Kit (Macherey-Nagel, Germany) and quantified with a DeNovix spectrophotometer (DeNovix, USA). The 16S rRNA V3/V4 region was amplified from 12 ng DNA using KAPA HiFi polymerase (Roche, Switzerland) and purified with AMPure XP beads (Beckman Coulter, USA). Libraries were dual-indexed with Nextera XT (Illumina, USA), checked for size and purity via Bioanalyzer (Agilent Technologies, USA), quantified with Qubit (ThermoFisher, USA), and sequenced (300 bp paired-end) on an Illumina MiSeq (Illumina, USA) using the MiSeq Reagent Kit v3.

Bioinformatics and Statistics

FastQC software was used to determine the quality of NGS reads which were further trimmed by trimmomatic and filtered based on their size by BBTools. Reads were analyzed with QIIME v1.9.1 (version 1.9.1). Forward and reverse reads were merged using fastq-join, and OTUs were identified through open-reference picking against the GreenGenes database (97% similarity). Unmapped sequences were clustered *de novo* and aligned. ChimeraSlayer was used for PCR chimeras' detection. NGS reads normalization was performed using metagenomeSeq's CSS (cumulative sum scaling) transformation.

Alpha- and beta-diversity metrics were analyzed, with beta diversity visualized through PCoA plots generated by PhyloToAST, and abundance plots created using the phyloseq package in R. Statistical tests included Mann–Whitney U for alpha diversity, nonparametric *t*-tests for taxonomy comparisons, and ANOSIM for categorical analysis. Functional predictions were made with PICRUSt, using GreenGenes for closed OTU picking and KEGG for pathway annotation. Metagenomic profile analysis and visualization were conducted with STAMP software. Statistical analysis and data visualization were also performed using STAMP.

Results

A total of 50 patients with AD (30 men and 20 women, mean age 29.5 ± 8.1 years) and 25 healthy controls (12 men and 13 women, mean age 29.3 ± 4.3 years, $p > 0.05$) were enrolled in the study. Disease severity was higher in men than in women (EASI score: 21.4 ± 17.8 vs 10.7 ± 8.6 , respectively; $p = 0.019$). The mean total serum IgE concentration in the study group was 1307.3 ± 1103.6 IU/mL. Elevated total IgE serum concentration was observed in 38 out of 50 patients (76%), with very high IgE levels present in 26 out of 50 patients (52%).

The composition of the stool microbiota, including major phyla, families, and genera, is graphically depicted in Figure 1. In both AD patients and healthy controls, *Bacteroidaceae* was the most dominant family, with *Bacteroides* as the most abundant genus. No significant differences were observed in alpha and beta diversity between patients with AD and healthy controls.

Alpha Diversity of the Gut Microbiota Increases with AD Severity and Total IgE Serum Concentration

In patients with AD, adjusted analyses revealed that the alpha diversity of the gut microbiota varied significantly between groups characterized by different disease severities and total IgE serum concentrations. Specifically, all measures of alpha diversity (Chao1, PD, and Shannon index) were lower in patients with mild AD compared to those with severe AD, as assessed by the EASI score. Additionally, Chao1 showed significant differences between patients with moderate and severe AD (Figure 2).

Alpha diversity was also higher in patients with elevated total IgE serum concentrations compared to those with normal IgE levels, as measured by the Shannon index (Figure 3). Furthermore, significant differences were observed in Chao1 between patients with normal IgE levels and those with elevated IgE levels. Finally, Chao1, and Shannon indices showed significant differences between patients with elevated total IgE serum concentrations and those with very high IgE levels (Figure 3).

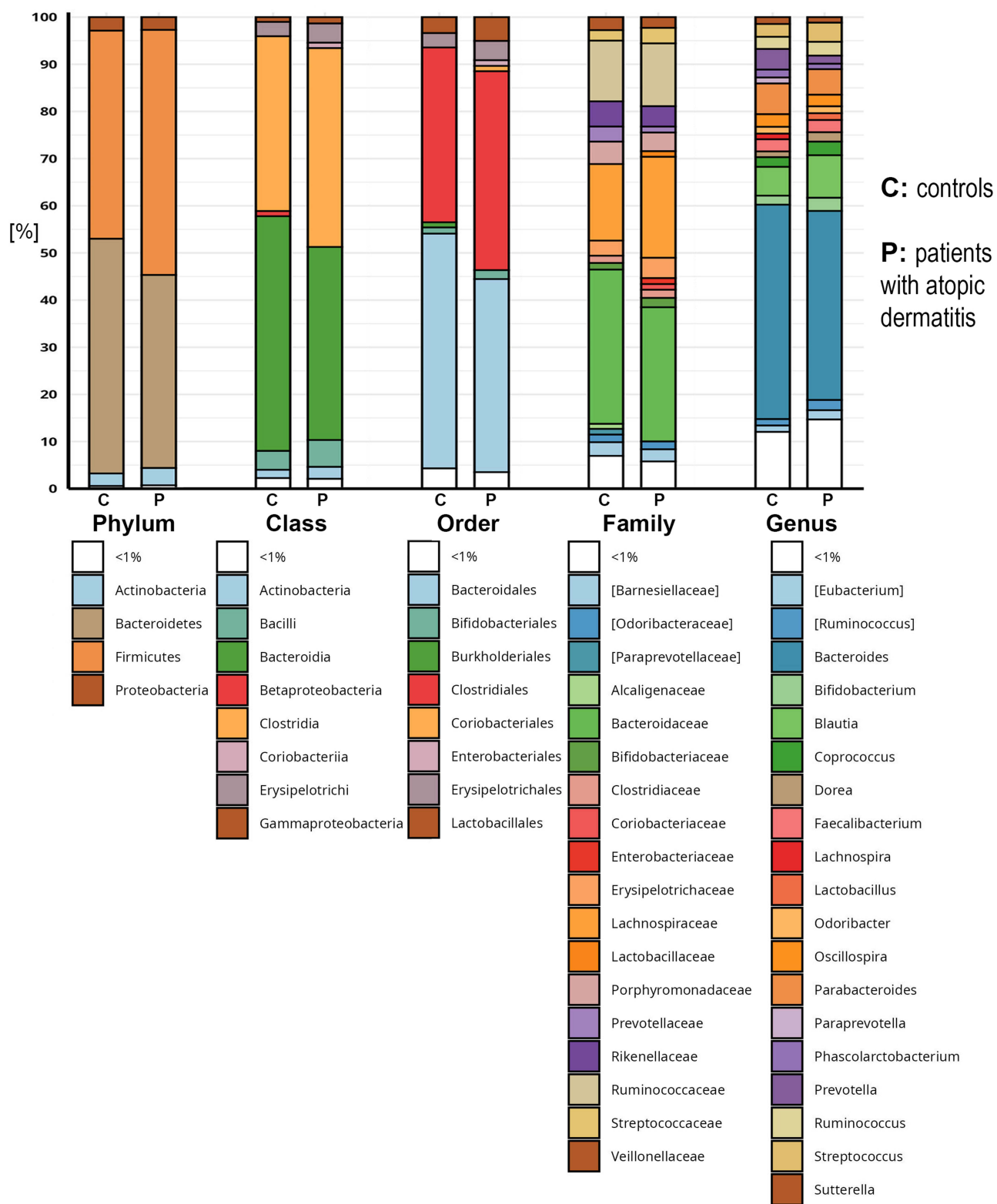


Figure 1 Gut microbiota composition in atopic dermatitis patients and healthy controls. Relative abundances above 1% at various bacterial taxonomic levels were visualized.

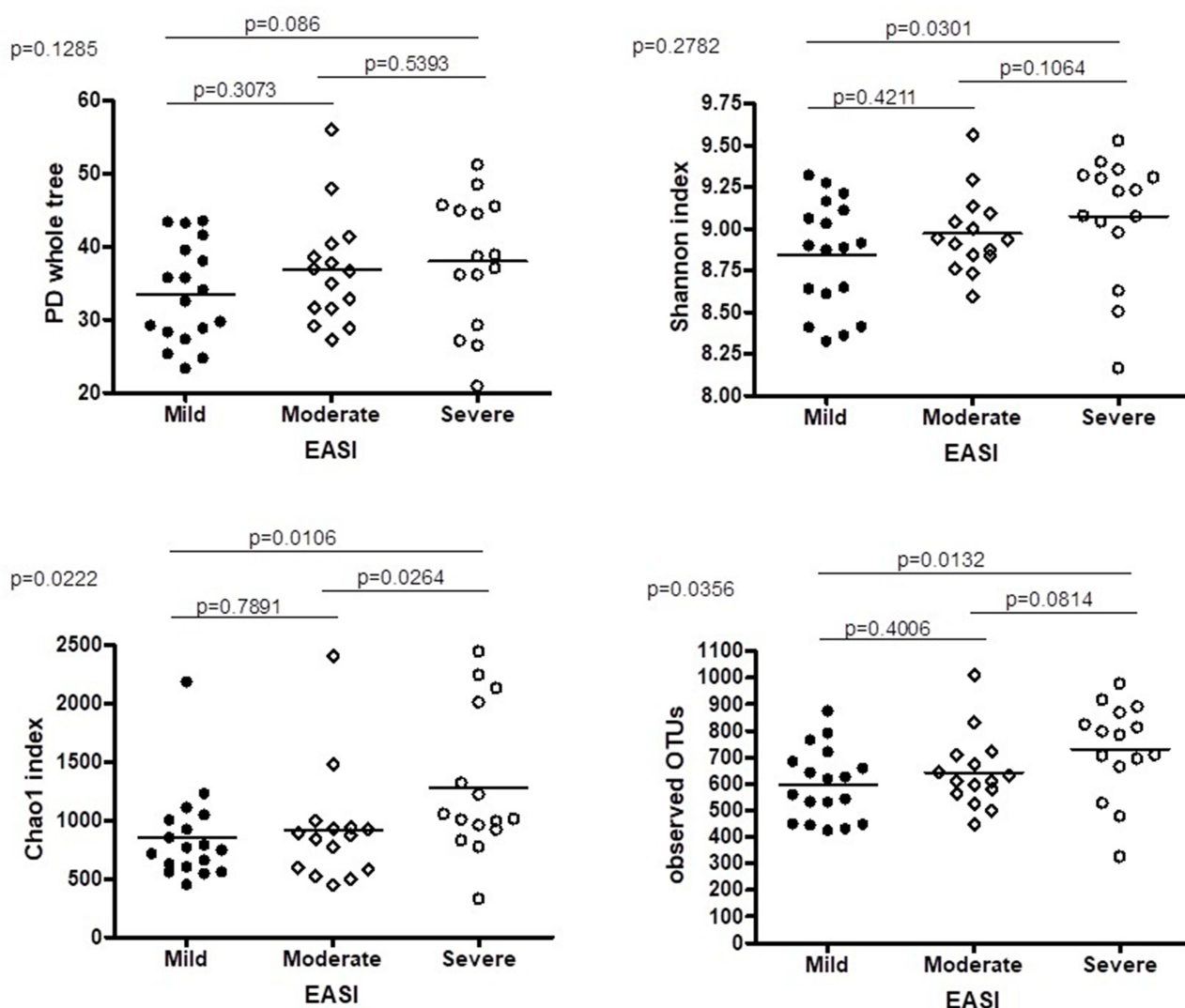


Figure 2 Alpha diversity metrics in patients with mild, moderate, and severe atopic dermatitis based on the Eczema Area and Severity Index (EASI).

Predicted Differential Impact of Gut Microbiota on Functional Pathways in Patients with Atopic Dermatitis Compared to Healthy Controls

PICRUSt analysis revealed significant differences in 149 KEGG pathways related to metabolism, genetic information processing, environmental information processing, organismal systems, and human diseases between the AD group and the controls (Figure 4a).

Energy metabolism was notably downregulated in patients with AD compared to controls (Figure 4b). Specifically, pathways such as oxidative phosphorylation and nitrogen metabolism were reduced, while the metabolism of ketone bodies was enriched (Figure 5). Several amino acid biosynthesis pathways—including those for beta-alanine, taurine, hypotaurine, glycine, serine, threonine, D-glutamine, and D-glutamate—were downregulated. Conversely, the lysine degradation pathway was upregulated. Predicted impairments were also observed in nucleotide and pyrimidine metabolism (Figures 4b and 5).

In addition, numerous significant differences were found in lipid and carbohydrate metabolism pathways. In the AD group, the most significantly upregulated lipid metabolism pathways involved the metabolism of fatty acids, ether lipids, glycerolipids, and glycerophospholipids (Figure 5). Regarding carbohydrate metabolism, a downregulation of the citric

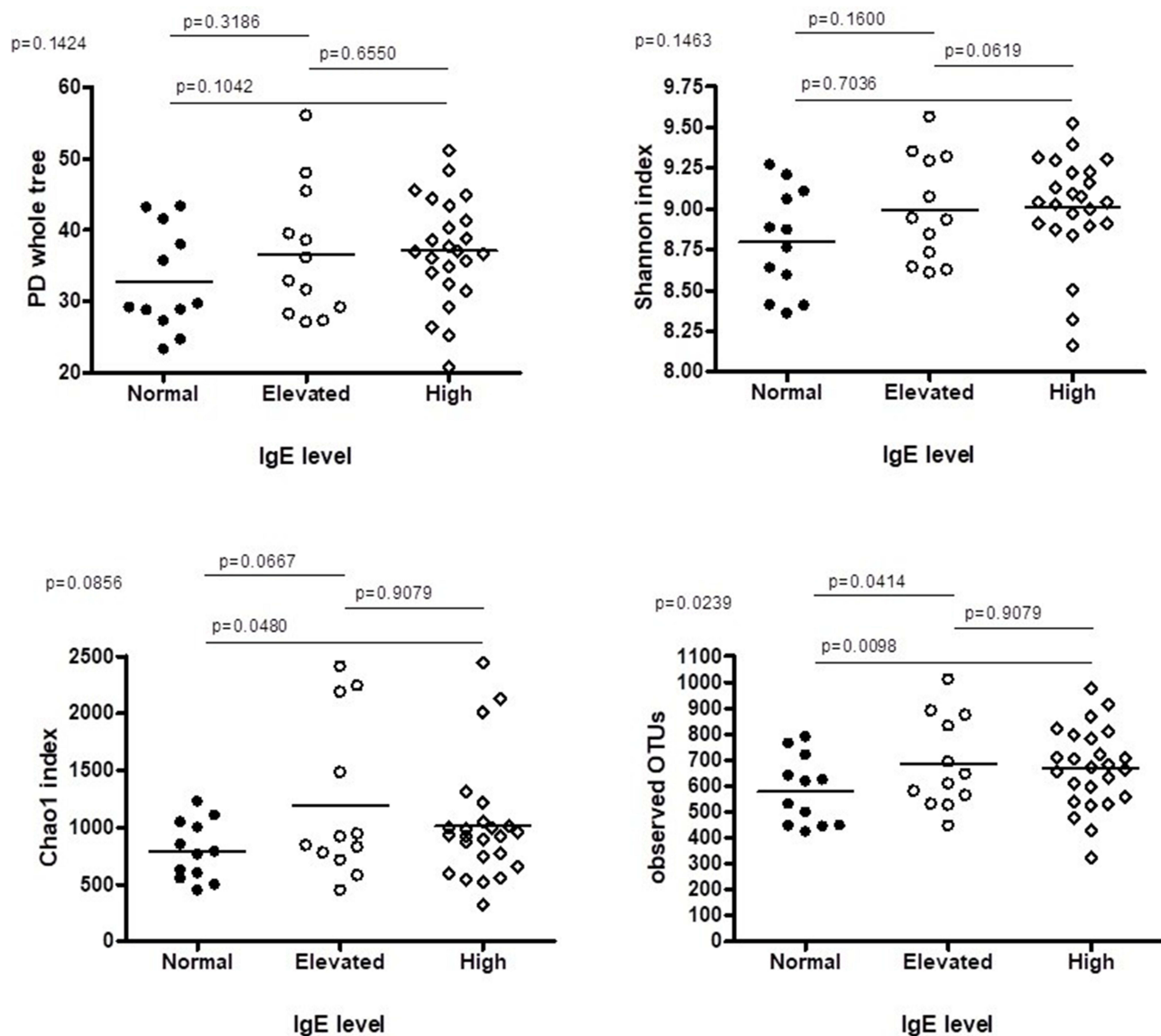


Figure 3 Alpha diversity metrics in atopic dermatitis patients with normal versus elevated IgE levels.

acid cycle was accompanied by an enrichment of glycolysis and the pentose phosphate pathway. Patients with AD also exhibited downregulation in the metabolism and biosynthesis of various cofactors and vitamins.

Key cellular processes and genetic information processing pathways were also downregulated in patients with AD compared to controls. These included pathways involved in transcription, translation, protein folding, replication, and DNA repair (Figures 4b and 6). Additionally, significant predictions were made regarding impairments in cell division, cell growth and death, and cell motility (Figure 4b).

With respect to immune and environmental signal processing, there was a significant increase in signal transduction pathways, including those involving protein kinases and RIG-I-like receptor signaling (Figure 7). In contrast, pathways related to antigen processing and presentation, as well as NOD-like receptor signaling, were downregulated. AD patients also exhibited reduced activity in peroxisome proliferator-activated receptor (PPAR) signaling and adipocytokine signaling pathways.

Among the human disease-related pathways, the most significantly enriched in AD patients compared to controls was the pathway associated with epithelial invasion by bacterial cells.

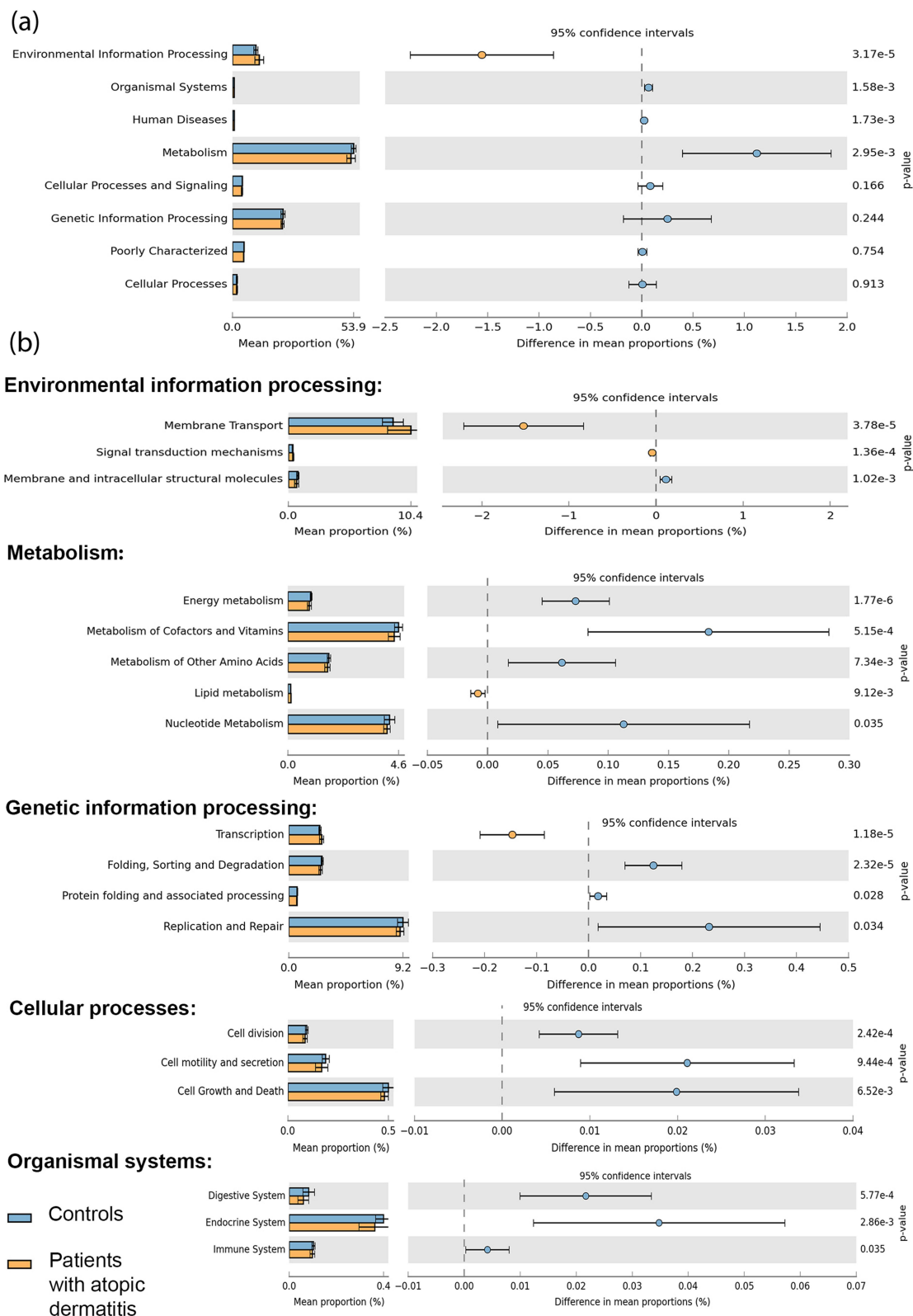


Figure 4 Statistically significant differences in Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) predictions between atopic dermatitis patients and healthy controls. Key alterations in Level 1 (a) and Level 2 (b) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways are visualized.

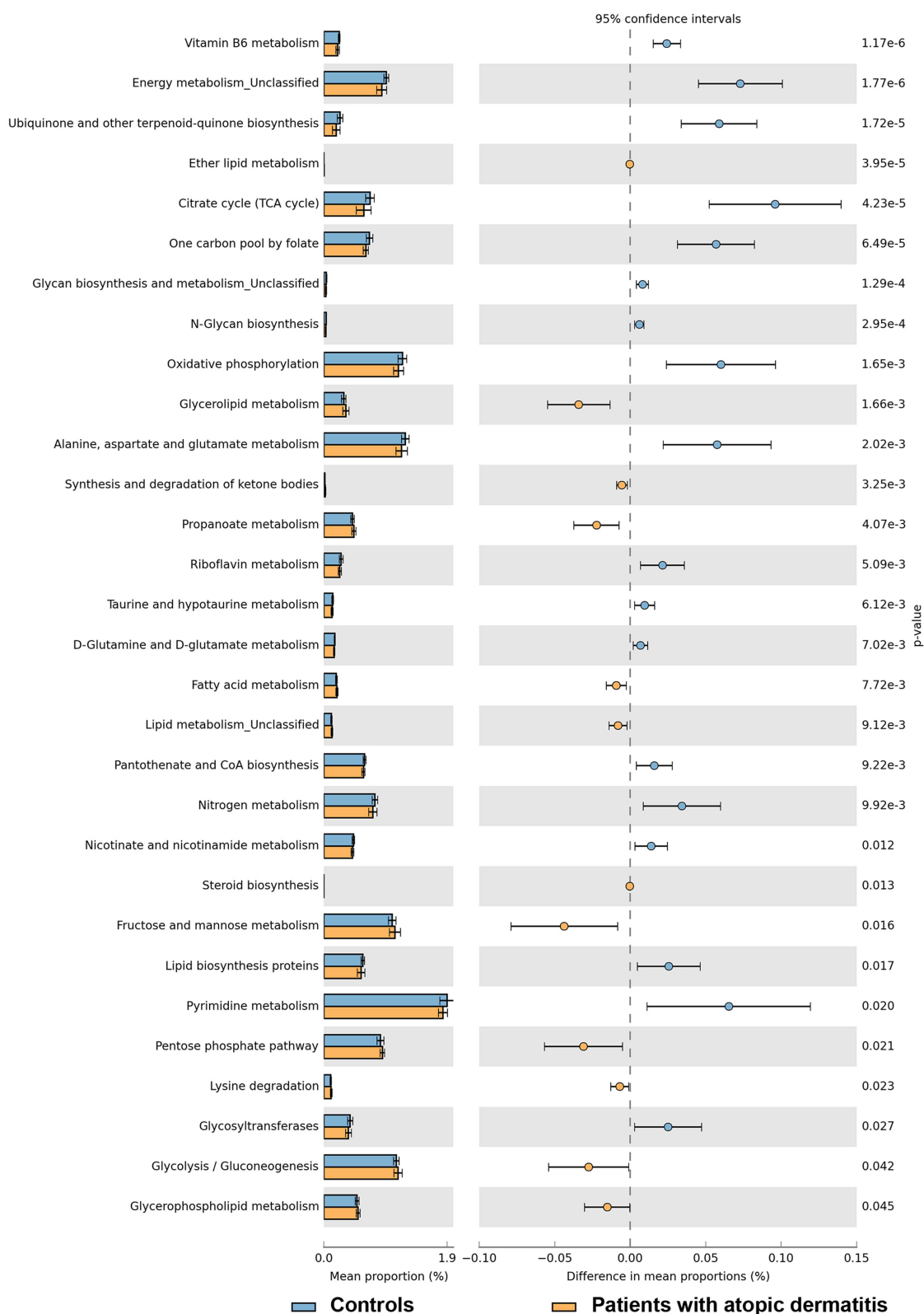


Figure 5 Statistically significant differences in Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) predictions between atopic dermatitis patients and healthy controls. Key alterations in Level 3 metabolic pathways are visualized.

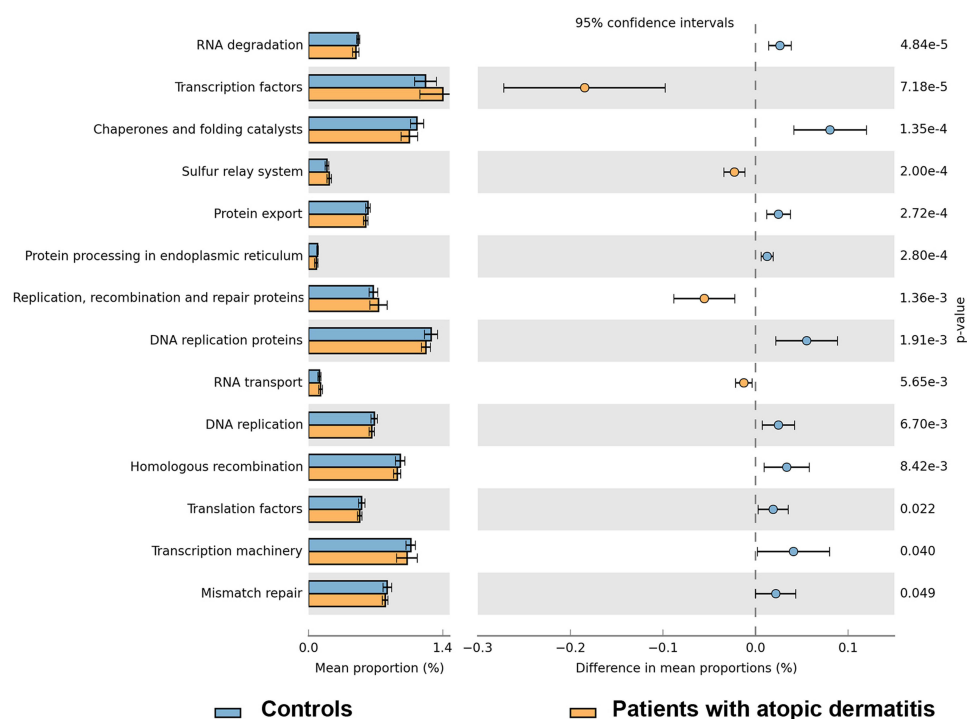


Figure 6 Statistically significant differences in Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) predictions between atopic dermatitis patients and healthy controls. Key alterations in Level 3 genetic information processing pathways are visualized.

Pathway Alterations Vary with Disease Severity and IgE Levels in AD Patients

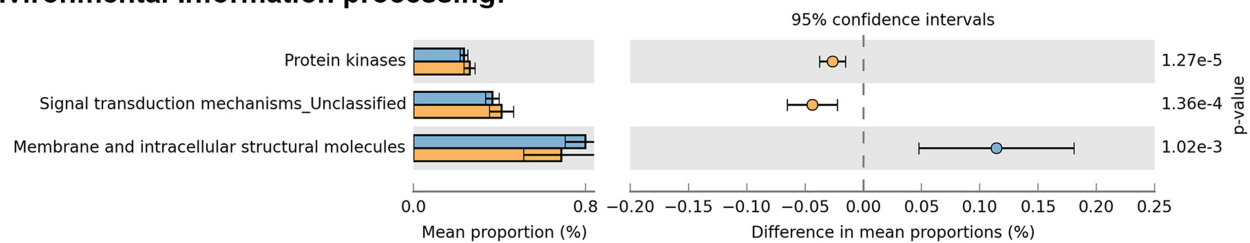
When restricting the analysis to the study group, significant pathway differences were observed in patients with varying clinical characteristics. Notably, a progressive enrichment in the alpha-linoleic acid metabolism pathway, biosynthesis of siderophore group nonribosomal peptides, and glyoxylate and diglyoxylate metabolism was identified as disease severity increased according to the EASI score (mild, moderate, and severe AD) (Figure 8a). On the other hand, the pentose phosphate pathway showed a progressive decrease with increasing disease severity. Additionally, several metabolic and immune pathways were altered in patients with elevated total IgE serum concentrations compared to those with normal total IgE (Figure 8b). These included ion channels, metabolism of cofactors and vitamins, cell division, pentose phosphate pathway, oxidative phosphorylation and biosynthesis of siderophore group nonribosomal peptides.

Discussion

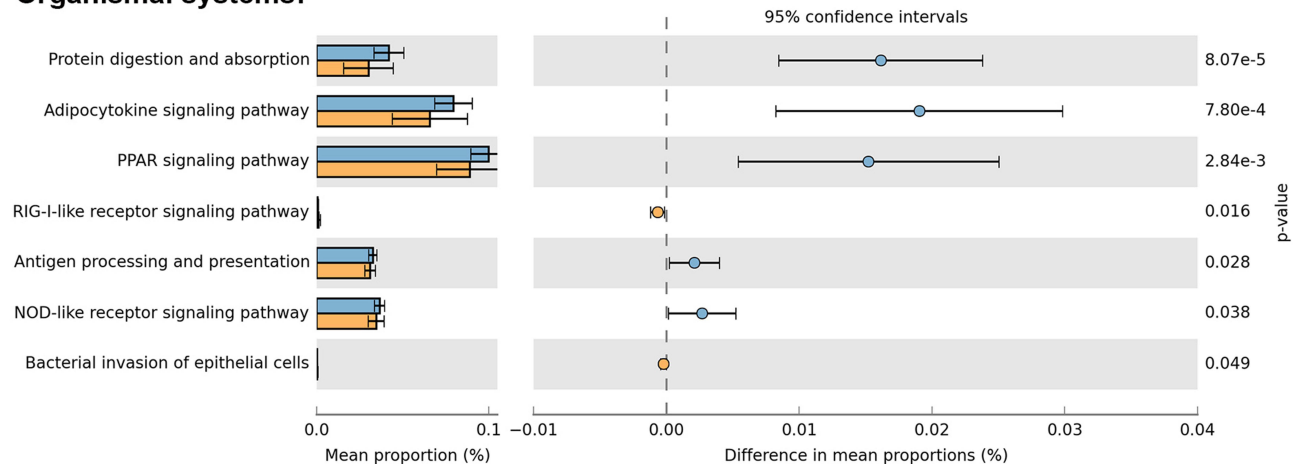
The role of the gut microbiota in inflammatory dermatoses is increasingly recognized.¹¹ Next-generation sequencing of the 16S rRNA subunit has shown great potential for identifying predictive biomarkers for these diseases.¹² However, most studies focusing on AD have primarily been conducted in children.⁶ Their findings are largely inconsistent, with varying degrees of bacterial richness, evenness, and the predominance of certain taxa in populations at an increased risk of developing AD. These discrepancies likely arise from differences in study design, as well as the diverse characteristics of the populations being analyzed. There is a relative paucity of reports linking gut microbiota composition to the course of AD in adults.⁸ This gap may be due to the prevailing assumption that the gut microbiota undergoes its most significant changes during the first years of life, with less dynamic shifts occurring in adulthood.¹³ Therefore, it is implied that any interventions targeting gut microbial imbalance should preferentially focus on infants to have a significant long-term effect. However, analyses of adult patients with AD could also provide new information on the microbiome-host interactions and contribute to questioning this paradigm.

This study found no significant differences in gut microbiome diversity between adults with AD and healthy controls, aligning with some previous reports.⁸

Environmental Information processing:



Organismal systems:



Cellular processes:

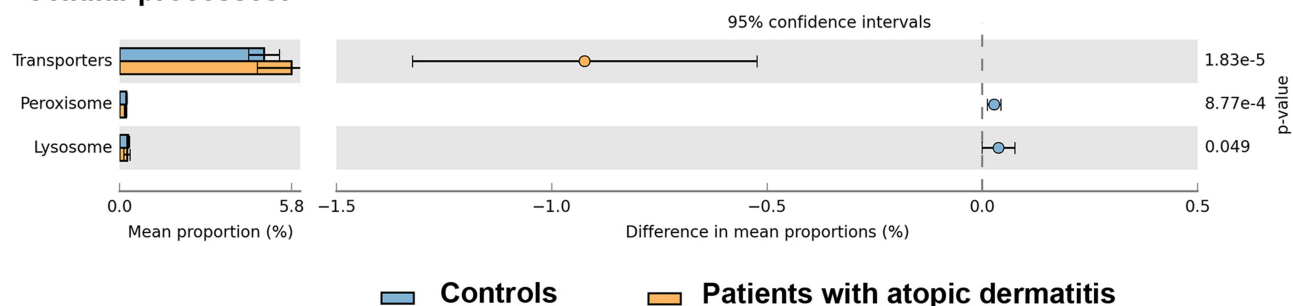
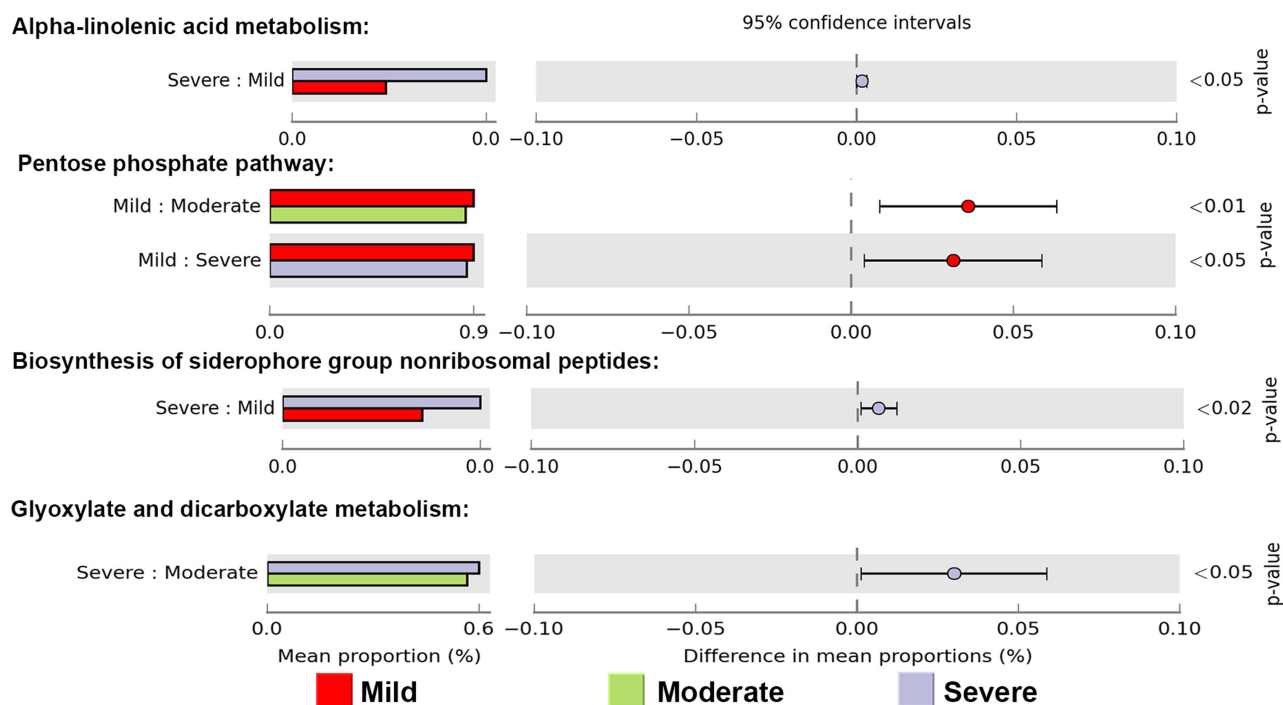


Figure 7 Statistically significant differences in Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) predictions between atopic dermatitis patients and healthy controls. Key alterations in Level 3 environmental information processing, organismal systems and cellular processes pathways are visualized.

Within the AD cohort, alpha diversity was positively associated with disease severity, as measured by EASI and was higher in individuals with elevated total IgE levels compared to those with normal levels. Although increased microbial diversity is generally associated with enhanced immune homeostasis, this relationship is not universally applicable. For example, Fazlollahi et al found that children with egg allergy or egg sensitization showed higher alpha diversity compared with controls.¹⁴ Their metagenomic analysis indicated that this increase may stem from altered nucleotide metabolism, leading them to propose that sensitization could be linked to specific bacterial metabolites and strains. These findings align with our previous work showing associations between food sensitization, total serum IgE levels, and microbial metabolites such as short-chain fatty acids and indoxyl.¹⁵ The association between alpha diversity and disease states also varies across other groups of conditions. For instance, decreased alpha diversity has been reported in Alzheimer's disease, while increased diversity has been observed in anorexia nervosa.¹⁶ These findings indicate that microbial diversity alone is an insufficient marker of health or disease. Accordingly, interpreting 16S rRNA sequencing results within clinical contexts requires complementary analyses to elucidate the functional implications of specific microbial taxa and their mutual relations on host physiology.

(a)



(b)

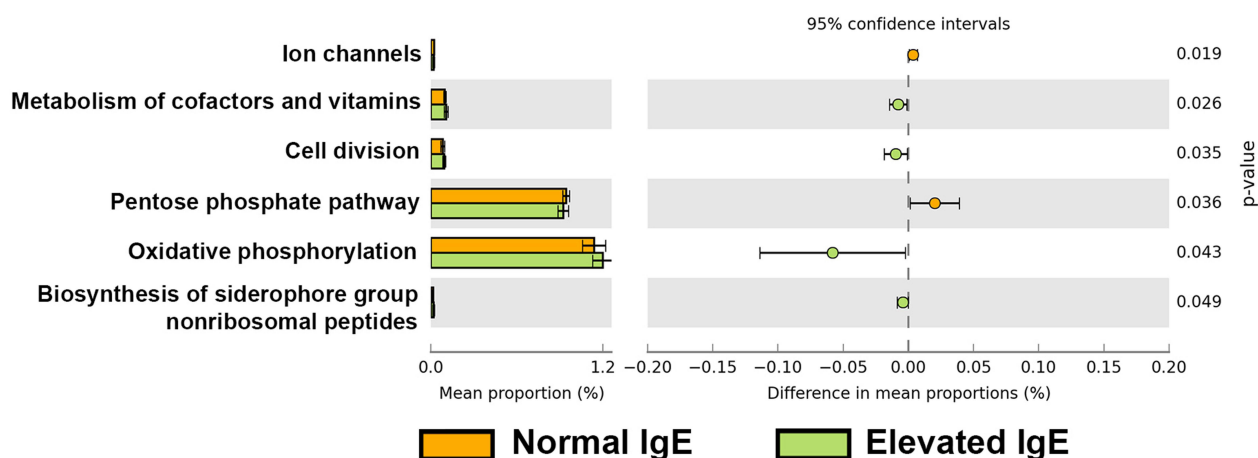


Figure 8 Statistically significant differences in Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) predictions between patients with varying disease severities based on Eczema Area and Severity Index (EASI) (a) and elevated versus normal IgE levels (b) are shown.

Standard 16S rRNA profiling workflows typically lack functional predictions. However, PICRUSt offers a useful approach for inferring microbial function.¹⁷ It clusters phylogenetically diverse taxa by functional similarity and relates them to specific environments. Its reliability has been supported by metagenomic comparisons, showing over 90% accuracy.¹⁸

In this study, PICRUSt analysis revealed that AD patients exhibited upregulated pathways of carbohydrate and lipid metabolism, alongside downregulated nucleotide and amino acid metabolism. These shifts could hypothetically contribute to immune dysregulation and impaired skin barrier function. The enrichment of lipid and carbohydrate metabolism pathways is particularly relevant, as it may promote immune activation and favor type 2 inflammatory responses.¹⁹

Th2 cell differentiation relies heavily on glycolysis, a pathway significantly enriched in the AD group.²⁰ Subsequent expansion and activation of tissue-resident Th2 cells are supported by upregulated lipid metabolism, particularly fatty acid pathways, potentially sustaining Th2-driven inflammation.²¹ Therefore, the upregulation of key effector cells and mediators (eg IL-4, IL-5, IL-13, and IL-31) may be associated with gut-microbiome-related alterations in carbohydrate and lipid metabolism. Interestingly, the relationship between metabolic abnormalities and immune dysregulation appears to be bidirectional, as IL-4 has been shown to influence glucose and lipid metabolism as well as regulate insulin sensitivity.²² To date, only one other study by Díez-Madueño et al has reported comparable microbiome-associated metabolic alterations in AD, notably a relative downregulation of energy metabolism, consistent with our findings.²³

Alterations in nucleotide and amino acid metabolism observed in the study group could also impact immune responses and barrier function. Nucleotides, especially pyrimidines, are crucial for energy metabolism and cell proliferation, processes essential for maintaining cutaneous homeostasis in AD. Although our study did not confirm such a correlation, this possibility is supported by previous findings showing that upregulation of the pyrimidine pathway has been associated with favorable responses to dupilumab treatment.²⁴ Additionally, beta-alanine contributes to carnosine synthesis, a dipeptide with antioxidant properties that supports skin integrity.²⁵ Taurine modulates ceramide expression and hyaluronic acid metabolism, thereby enhancing barrier function.²⁶ In experimental allergic inflammation, taurine supplementation reduced NF- κ B signaling and thymic stromal lymphopoietin levels, demonstrating immunomodulatory effects.²⁷ Glycine and serine were downregulated in a mouse model of delayed-type hypersensitivity mediated by Th1 and Th17 cytokines.²⁸ These cytokines co-express with type II inflammatory mediators in chronic AD and various endotypes, including Asian and pediatric populations.⁴ In a murine AD model, glutamine supplementation reduced their expression.²⁹

Consistent with our findings, Díez-Madueño et al linked gut microbiota composition to downregulated amino acid biosynthesis pathways in patients with AD compared to healthy controls.²³ In contrast, Liu et al reported an enrichment of the L-histidine biosynthesis pathway in patients with AD and an enrichment of the L-histidine degradation pathway in healthy controls.³⁰ This finding is somewhat perplexing, given that L-histidine has been shown to alleviate AD symptoms, likely by enhancing skin barrier function through the upregulation of filaggrin biosynthesis.^{31,32}

Immune-related pathways reduced in the AD group included NOD-like receptor signaling and antigen processing and presentation, while signal transduction pathways and protein kinases were enriched. The downregulation of NOD-like receptor signaling alongside the upregulation of bacterial invasion of epithelial cells, could partially underlie the increased susceptibility to cutaneous infections observed in patients with AD.^{33–35} In contrast, the enrichment of signal transduction pathways, including protein kinases involved in regulating immune responses and cellular proliferation (eg JAK-STAT and NF- κ B), could hypothetically reflect the immune dysregulation observed in AD.³⁶ Furthermore, compared to controls, the AD group showed distinct alterations in pathways related to DNA repair, transcription, translation, and protein folding, sorting, and degradation. These differences could suggest a potential connection between core cellular processes and downstream effects on epidermal barrier integrity and immune function in AD.³⁷ For example, impaired degradation of endogenous RNA may lead to upregulation of the RIG-I signaling pathway, as observed in our study group.³⁸ This conserved pathway is associated with cellular stress responses and the activation of inflammation to detect and eliminate defective or infected cells.³⁸ Notably, no previous functional studies of the gut microbiota in AD have reported alterations in the specific immune-related and cellular pathways identified in our analysis.

As anticipated, PICRUST predictions revealed the most pronounced differences between AD patients and healthy controls. However, several pathways also varied significantly with AD severity and IgE status. Increased disease severity was associated with enrichment in pathways such as alpha-linolenic acid metabolism, siderophore group nonribosomal peptide biosynthesis, and glyoxylate/dicarboxylate metabolism, while the pentose phosphate pathway was reduced. Alpha-linolenic acid, known for its immunomodulatory properties, has been reported at elevated levels in AD, although its metabolites are often diminished.³⁹ These findings appear to suggest further dysregulation of lipid metabolism in AD, potentially exacerbating immune imbalance. Likewise, the upregulation of siderophore metabolism may reflect underlying iron deficiency, which has been shown to support the survival of Th2 cells.⁴⁰ The glyoxylate/dicarboxylate metabolism pathway has not been previously associated with AD. However, its enrichment could hypothetically indicate dysregulated processing of toxic metabolites, akin to that seen in primary hyperoxalurias.⁴¹ In contrast, the

downregulation of the pentose phosphate pathway critical for fatty acid, purine, and pyrimidine metabolism could be linked impaired mechanisms of immune tolerance.⁴²

Patients with elevated IgE levels exhibited similar PICRUSt-predicted changes, including enrichment of siderophore group nonribosomal peptides and reduced pentose phosphate metabolism. Additionally, pathways related to cell division, oxidative phosphorylation, and the metabolism of cofactors and vitamins were enriched, while the ion channel pathway was downregulated. Previous report suggest that upregulation of cell division and oxidative phosphorylation could reflect heightened inflammatory activity, as these processes support the energy demands of plasmacyte proliferation.⁴³ In turn, alterations in ion channel pathways could reflect changes in intracellular signaling that promote type II inflammation.⁴⁴ The metabolism of vitamins and cofactors, known to be influenced by gut microbiota, also affects immune function,⁴⁵ with changes in vitamin metabolism reported in metagenomic study by Díez-Madueño et al.²³ We did not observe differences in branched-chain amino acid pathways between patients with elevated and normal IgE levels, although previous PICRUSt analyses have reported such differences between extrinsic and intrinsic AD subtypes.³⁰ However, this discrepancy may be attributed to various confounding factors, including differences in the study population and design.

Our data underscore the value of incorporating functional analyses into studies of gut microbiota composition in AD. This approach may offer deeper insights into how the microbiota influences host physiology, although its translational relevance remains to be fully established. To date, studies on probiotic supplementation in AD have yielded inconsistent results.⁴⁶ Post hoc analyses of existing datasets, together with carefully designed future investigations, may help identify microbial strains that support immune and metabolic homeostasis. Such findings could eventually inform the development of targeted probiotic candidates, but any therapeutic application will require rigorous validation.

Limitations

Our study is limited by its cross-sectional design, which precludes causal inference between the observed variables. Although the predicted functional changes align with known mechanisms of AD pathogenesis, such as barrier dysfunction and type II inflammation, these associations cannot be confirmed with the current data. Given the complex and heterogeneous nature of AD, potential links between the gut microbiota and disease should therefore be interpreted with caution. Furthermore, we have not stratified analyses based on potential confounding factors, such as body mass index, diet and recent infections.

Conclusion

This study investigated the gut microbiota in adult atopic dermatitis patients by assessing microbial diversity and predicting functional impacts on immune and metabolic pathways using 16S rRNA sequencing and PICRUSt analysis.

Although no significant differences in overall microbiome composition were observed between atopic dermatitis patients and healthy controls, PICRUSt suggested alterations in several metabolic, cellular, and immune-related pathways. Notably, predicted upregulation of carbohydrate and lipid metabolism may reflect shifts that coincide with features of immune activation and type 2 inflammation. Furthermore, predicted disruptions in amino acid and nucleotide metabolism, together with decreased activity in pathways such as NOD-like receptor and PPAR signaling, could be consistent with processes affecting immune tolerance and barrier function. However, we acknowledge that these potential associations were not confirmed in the present study and should be examined in future research.

Our findings highlight the complexity of gut–skin interactions and underscore the need for longitudinal, multi-omics studies to better clarify how microbiome-related functional changes relate to AD pathophysiology. Such approaches may eventually help inform the development of novel interventions such as targeted probiotic supplementation that could support disease management.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author (Leszek Blicharz) on reasonable request.

Ethics Approval and Informed Consent

The research conformed to the principles of the World Medical Association's Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Medical University of Warsaw (approval no. KB/141/2020 with subsequent amendments). All participants provided written informed consent prior to enrollment in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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