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Research Article

UTILIZING ADVANCED BIOINFORMATICS TECHNIQUES TO DEVELOP A GENETIC AND EPIGENETIC UNDERSTANDING OF ATOPIC DERMATITIS

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Abstract

Atopic Dermatitis has been a chronic and inflammatory condition. This chronic skin condition has been linked to future atopic-associated conditions such as asthma, allergic rhino-conjunctivitis, and food allergy. The mutated FLG along with Interleukin genes has been considered as a causative factor in AD pathology. Bioinformatics technologies have revolutionized the study of AD, providing crucial insights into its molecular complexities. The review has navigated the key studies, focusing on methodologies from identifying Differential Expression Genes (DEGs) to applying Weighted Gene Co-Expression Network Analysis (WGCNA), Microarray analysis, Gene Ontology (GO) studies, and Protein-Protein Interaction (PPI) network. In the healthcare field, advancements in AD treatment options, including biologics such as Dupilumab, Tralokinumab, and Janus Kinase Inhibitors, signify a fundamental shift towards more targeted and effective approaches for AD treatment. Challenges persist in AD research, requiring a deeper understanding of the correlation between genetic and environmental factors, identification of specific biomarkers, and comprehension of immune cell infiltration. For addressing these challenges, the integration of emerging technologies like machine learning, personalized treatment strategies and multi-omics offer promising results. It is important to further navigate the specific genes associated with AD pathogenesis and bioinformatics tools to find better and more advanced treatment for the skin disease.

Keywords: Atopic dermatitis, Pathogenesis, Bioinformatics, Filaggrin, Genes, Treatment, Challenges.

INTRODUCTION

Atopic Dermatitis (AD), or Atopic eczema, has been a chronic, heterogeneous, and inflammatory condition. Patients with AD suffered from redness and itching on the skin with altered immune response [1]. This inflammatory skin condition could be due to genetic or epigenetic factors. Children afflicted with AD face a heightened risk of developing various health complications, including asthma and allergic rhinitis[1]. This chronic skin condition has been linked to future atopic-associated conditions such as asthma, allergic rhino-conjunctivitis, and food allergy [2]. Moreover, it extends its reach to non-atopic entities, stimulating associations with inflammatory diseases and psychological disorders [3]. The clinical presentation of AD is diverse, characterized by eczema-like eruptions that include erythema, papules, and exudative lesions, with distinct manifestations depending on the patient's age, childhood, or adulthood and varying degrees of skin dryness [4].AD's prolonged condition leads to chronic inflammation and skin thickening. Persistent itching has been a major symptom that significantly disrupts daily activities, causing insomnia and sleep disorders, ultimately diminishing the overall quality of life of AD patients [4]. In infants, AD often manifests as tiny bumps on the cheeks, while older children and adults commonly experience rashes in joints' folds, hands' backs, or the scalp [5]. Prevalence of this disease occurs mostly in infancy or early childhood. In Germany, the 1-year prevalence of AD among children is 28% [6]. The prevalence varies worldwide, with the highest prevalence in Sweden, United Kingdom, Iceland, Finland, and Denmark, and the lowest in Uzbekistan, Armenia, Tajikistan, China, and Kyrgyzstan [7, 8].

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AD at its initial stage is also called Atopic march, which leads to the progression of several disorders in infants [9]. AD is a chronic, systemic, and inflammatory disease that significantly impacts patients' lives, causing physical, psychological, and socioeconomic burdens [10]. A study of over 1500 adults and adolescents found that 76% and 69% of patients had moderate-to-severe AD, respectively, indicating inadequate management of their symptoms. Severe itching was reported by 43% and 35% of patients, with a significant impact on quality of life [11]. The global prevalence of AD and the population affected by AD were estimated to be 2.6% and 204.05 million people, respectively. Females were more likely to suffer from AD than males, with a global prevalence of 2.8% in females and 95.76 million in males, respectively. Globally, the prevalence rates of AD have been estimated in adults, around 101.27 million while in children 102.78 million with a 2.0% (95% UI 1.4–2.6) and 4.0% (95% UI 2.8–5.3), respectively [12].

Genetic Factors in AD

Polymorphisms in Genes of Epidermal Barriers

The epidermis has always been a first line of defence, separating the host from its surroundings, specifically the stratum corneum layer (SC) which is the end product of a complex keratinocyte differentiation process [13]. Tight junctions, corneodesmosomes, and the SC matrix combine to develop a strong and flexible physical barrier that reduces water loss and shields the body from microbial and allergen infiltration [14]. Several studies reported that the loss of function occurs due to the gene named Filaggrin (FLG) mutations, which have been a well-replicated and significant risk factor for AD development. The mutated FLG has been recognized as a causative factor in AD development [13]. According to recent research, deficiencies in terminal

keratinocyte differentiation that result in lower levels of ceramides, FLG, and antimicrobial peptides play a significant role in developing skin inflammation in AD patients [15].

Filaggrin Mutations

FLG, a crucial structural protein in the stratum granulosum of the skin, made a major contribution to the natural moisturizing factor (NMF). As compared to patients with AD without FLG mutations (ADNON-FLG), patients with FLG mutations (ADFLG) suffer from severe and persistent disease, more cases of AD herpeticum, and a higher risk of several asthma and allergies [16]. The key genetic factor of AD has been the presence of Loss-of-Function (LoF) mutations in the FLG. The research estimated the odds ratio between FLG and AD to fall within the range of 3.12 to 4.78, with maternal FLG mutations independently increasing the risk of AD inheritance [17]. Patients with moderate to severe AD have been shown to have associations with major components of NMF, trans-UA and PCA, which are breakdown products of FLG and act as reliable surrogate markers for FLG genotype. Additionally, FLG mutations have been linked to stratum corneum interleukin-1 (SC IL-1) cytokines in ADFLG patients, suggesting a preexisting or higher pro-inflammatory status in their skin [16, 18].

Serine protease inhibitor Kazal-type 5 (SPINK5) Mutations

It is located in serine peptidase. An SPINK-5 inhibitor known as lympho epithelial Kazal-type-related inhibitor (LEKTI) is encoded by the cluster inhibitors gene on chromosome 5q31 [19]. LEKT1 regulates proteolysis in keratinocyte differentiation and normal epithelium. Mutations in SPINK5 have been associated with AD, particularly in eastern Asians[20]. According to research, the path ophysiology of AD was better understood by using the LEKTI-deficient mouse model, in which protease-activated type 2 receptor (PAR2) binds to kallikrein 5 and stimulates the production of TSLP (thymic stromal lymphopoietin) in an NFκB-dependent manner [21].

Immune Response and Stress Regulators (PRRs)

PRRs protect from microbial pathogens by recognizing molecular patterns associated with pathogens [22]. PRRs mutations such as toll-like receptors or TLRs and nucleotide-binding oligomerization domain-like receptors (NOD or NLRs), including NALP1, NALP12, CARD4, CARD12, CARD15, and NOD1, have been associated with AD [23]. Severe AD patients have TLR2 polymorphisms, TLR4 mutations, TLR6 polymorphisms, TLR9 promoter polymorphisms, and several NLR gene polymorphisms[24]. SNPs of the human β-defensin 1 gene have also been associated with AD [25].

Mutations in Other Genes

In AD, thymic stromal lymphopoietin or TSLP, is over expressed on the epidermis, primarily produced by keratinocytes and other skin cells. TSLP carries out its activities by binding to a heterodimeric receptor made up of the TSLP receptor chain (TSLPR) and the IL-7 receptor alpha chain (IL-7Rα)[26, 27]. Genetic polymorphisms in the alpha chain of the high-affinity receptor for IgE (FCERIA) have been linked to AD. AD and elevated serum levels of total IgE have been linked to SNPs in the FCERIA promoter region[26, 28]. The FCERIA gene plays a significant role in the IgE response and allergic sensitization, supported by a large and replicated GWAS [28]. In AD, the increased expression of Th2 cytokines and Th22 cytokine, IL-22 have been associated with the adaptive immune response [29]. Several distinct polymorphisms of IL4, IL-5, IL-13, IL-4 receptor alpha, IL-5 receptor alpha, and IL-13 receptor alpha have been found to influence susceptibility to AD in different populations [30]. In clinical trials, vitamin D has been connected to improved eczema control and is necessary for cutaneous immunity. According to a study, rs4674343 in CYP27A1 is linked to AD in Southern Chinese people. GC rs7041 and CYP2R1 rs7935792 interacted to modify total IgE, and CYP2R1 and VDR haplotypes changed eczema susceptibility [31]. However, several genes have been associated with the occurrence of AD. These genes fall into four categories, i.e., immune system-related genes, keratinocyte, stress response-related genes, genes that affect the disability of the skin's barrier of defence, and genes involved in vitamin D metabolism, as shown in Table I.

Table I. A comprehensive outline of key genes associated with the epidermal barrier, immune responses, stress modulation in keratinocytes, and the processing of vitamin D

Genes	Genetic Variation
Genes Related to the Epidermal Barrier	Filaggrin Gene (FLG) SPINK5 gene encodes the serine protease inhibitor LEKTI.
Genes Connected to Changes in Immune Responses	Mutations in pattern-recognition receptors (PRRs) like Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) are linked to AD.
Genes Associated with the Stress Response in Keratinocytes	TSLP and TSLPR genes are central to stress response in keratinocytes.
Genes Associated with Adaptive Immune Responses	polymorphisms of IL4, IL-5, IL-13, IL-4 receptor alpha, IL-5 receptor alpha, and IL-13 receptor influence susceptibility to AD
Genes Participating in the Processing of Vitamin D	CYP27A1, CYP2R1, VDR, and genomic region 20q13 (encompassing CYP24A1) linked to AD.

Understanding the association of AD with the above-mentioned genetic variables helps to address the complex nature of AD by providing useful information for developing individualized treatment plans and targeted interventions for affected individuals.

Epigenetic Modifications in AD

Epigenetics refers to variations in gene expression without impacting the DNA sequence constituting the epigenome [32]. These alterations occur in primary epigenetic mechanisms that control gene expression profiles in cellular processes such as DNA methylation, histone protein modification, and RNA-dependent non-coding regulation [33]. Epigenetics mechanism controls the expression of genes through histone modification, hydroxyl-methylation, methylation, the position of a nucleosome, and chromatin remodelling by ATP and RNA regulation [32]. In AD, the two major types of epigenetic modifications have been discussed below

DNA Methylation

A study on DNA methylation changes in AD identified methylation and gene expression at epidermal CpG sites in

lesional, non-lesional, and healthy control, T and B cells, and whole blood [34]. The study found that CpG methylation was unaffected in T and B cells and whole blood. Still, in the lesion epidermis of AD patients, increased expressions for S100A2, S100A7, S100A8, S100A9, and S100A15 (hyper-methylated) were observed, while KRT6A (decreased methylation) and KRT6B expressions were increased in keratinocytes. The FLG gene mutations, which are essential for maintaining skin barrier function, are a widely replicated genetic risk factor for AD. Other genes and loci contribute to AD pathogenesis, immune dysregulation, skin barrier function, and inflammatory responses. KIF3A gene variation is linked to pediatric asthma, while NLRP2 gene repression is linked to early-onset childhood AD. A functional single nucleotide polymorphism (SNP) controls cell type-specific methylation of the VSTM1 gene locus, which has been implicated in AD development. These genetic variations contribute to the pathogenesis of AD and contribute to the development of various diseases [1].

According to a study, subsets of CD4+ T and CD8+ T cells showed specific cell-type changes in DNA methylation [34]. Another study was conducted on the differences of DNA methylation by a chip-based method in CD4+, CD4+CD45RA+ naïve, CD8+ T cells and CD4+CLA+ in which ten hypo-methylated and 25 hyper-methylated genes influencing cytokine signalling pathways and immune inflammation (ARHGEF3, ASB2, DAPP1, IL10RA, PDE4A, SH2B3, STIM1, and TOX2) were discovered in AD patients. A relationship of decreased upstream methylation of IL13 and increased IL13 expression, suggesting potential epigenetic regulation for IL-13, a Th2 marker for AD. The immune response in AD has been influenced by various receptors, including IL-4Rα, IL-5Rα, and IL-13Rα1. These cytokines were involved in allergic inflammation and immune regulation, leading to inflammatory processes in AD. Dysregulation of the OX40-OX40L pathway can contribute to immune dysregulation. P2X3 receptor activation may cause itch sensation and neurogenic inflammation in AD, impacting sensory aspects. S1PR1 receptor signaling, involved in immune cell trafficking and inflammation, may also be affected by AD[35]. Several studies have investigated the distinct sites of CpG in DNA methylation, which leads to the involvement of several genes that cause AD. A study revealed that rs612529-T in the VSTM1 (SIRL-1) promoter is significantly associated with increased expression of allele-specific SIRL-1 in monocytes in healthy patients. The SNP rs612529T/C, located in the promoter of the VSTM1 gene, plays a significant role in influencing the methylation of the VSTM1 gene locus in different cell types, particularly monocytes. The T allele of this SNP facilitates the binding of transcription factors YY1 and PU.1, with PU.1 acting as a docking site for modifiers of DNA methylation. This allele-specific binding leads to a complete demethylation of the VSTM1 promoter, correlating with the upregulation of SIRL-1 expression in monocytes. This allele-dependent methylation pattern is hypothesized to be mediated by the recruitment of demethylases, such as Tet2, as a result of the allele-specific binding of PU.1 to rs612529. This SNP acts as a genetic master switch for the epigenetic control of SIRL-1 expression by CpG demethylation [36].

Histone Modifications

Diverse histone modifications have been significantly found in the genome of AD patients. Epigenetic marks of histone modification include phosphorylation, methylation, acetylation, and ubiquitination, which influence repression in a tissue-specific way or transcription activation [1]. Histone acetylation, methylation, phosphorylation, and ubiquitination are all crucial processes in gene regulation. Acetylation neutralizes histones' positive charge, allowing for more relaxed chromatin structure and increased accessibility of transcription factors. Methylation affects lysine or arginine residues and can recruit specific chromatin-modifying complexes. Phosphorylation affects chromatin structure and recruitment of transcriptional regulators, influencing gene expression. Ubiquitination marks histones for degradation or recruits' proteins to modify chromatin structure. Common histone modifications that identify active enhancers and transcriptional start sites (TSS) are H3K4me1 (mono-methylation of the fourth lysine on histone 3) and H3K4me3 (tri-methylation of the fourth lysine on histone 3) respectively [37]. A broad class of enzymes known as histone deacetylases, histone acetyltransferases, histone methyl transferases, and histone demethylases catalyze different modifications to histones, which collectively write an epigenetic mark on DNA [38]. Using antibodies specific to these epigenetic histone marks, chromatin immunoprecipitation can elucidate these markers [1].

Micro-RNA (miRNA)

miRNA plays a role in AD pathogenesis, as they inhibit mRNA via 3′ UTR binding transcripts and target HDAC and DNMT epigenetic regulators[39-41]. MiR-335 expression decreased in AD lesions compared to healthy skin [41]. High-throughput miRNA sequencing identified 25 differentially expressed miRNAs, with miR151a being the top miRNA upregulated in AD patients. IL12RB2 was predicted to be a target of miR-151a, and lentiviral transduction of miR-151a in Jurkat cells decreased IL12RB2 and other Th1 cytokines, IL-2, IL-12, and IFN-γ expressions. These findings identify miR-151 as a key miRNA in the pathology of AD [1].

Table II Summarizing the key points related to epigenetic mechanism in the context of AD

Aspect	Key Points
DNA Methylation	The TSLP gene experiences demethylation in AD lesions, leading to TSLP over expression and increased inflammation. Genome-wide DNA methylation in CD4+ T cells reveals distinct patterns in AD, with hypermethylation in psoriasis. CD4+CLA+ T cells exhibit specific DNA methylation changes associated with immune inflammation in AD. VSTM1 promoter demethylation results in upregulated SIRL-1 expression in AD susceptibility. The KIF3A gene displays distinct patterns of methylation related to AD susceptibility.
Histone Protein Modifications	Uniquely-mapped regions H3K4Me1, H3K27Ac, and H3K4Me3 HDAC activation in epithelial barrier dysfunction associated with AD.
miRNA	MiR-335 expression decreased in AD lesions. IL12RB2, a target of miR-151a, and lentiviral transduction of miR-151a decreased IL12RB2, Th1 cytokines, IL-2, IL-12 and IFN-γ expressions

Thus, understanding the epigenetic modifications in AD patients has been essential for developing customized treatment plans and new molecular classifications of AD.

Applications of Advanced Bioinformatics in AD Research

Identifying genetic variations in oncological research has extensively utilized bioinformatics tools for genetic data. Additionally, it has been essential in developing biomarkers for inflammatory diseases like AD.

Identification of DEGs (Biomarker Discovery)

Bioinformatics technology has revolutionized the study of AD. High-throughput technology, based on big data, allows researchers to extract related differential expression of genes (DEGs) from gene expression data. The process involves data cleaning and preprocessing, differential expression analysis, functional annotation, and pathway analysis. The screened disease and normal groups are compared, and DEGs related to the disease are screened. The bioinformatics analysis determines their biological functions and metabolic and signalling pathways. This approach helps identify DEGs and metabolic pathways associated with AD pathogenesis, revealing AD's pathogenesis and pathophysiological processes and providing new targets; [42, 43]. Several studies have investigated gene expression dysregulation in AD, revealing significant insights into its pathophysiology. According to this study, several gene expression profiles, including GSE121212, GSE5667, GSE120721, GSE32924, GSE36842, GSE58558, and GSE107361, acquired from the Gene Expression Omnibus (GEO) database [44]. The datasets were selected based on certain requirements, such as the use of microarray chip technology, comparisons of gene expression between lesional and nonlesional skin among AD patients, and a minimum sample size greater than [45]. Considering similar eligibility criteria, another study utilized the data for microarray from GSE6012, GSE32924, GSE36842, and GSE120721. The information from GSE32924 from 33 samples, including normal skin samples from healthy volunteers and lesional and nonlesional skin samples from AD patients [43].

WGCNA

WGCNA, or co-expression network analysis of weighted gene, is used to identify correlations between genes in biological networks. It has been applied in various studies to identify potential biomarkers or genes in AD and to compare AD patients with healthy populations. By identifying gene clusters with strong correlations, WGCNA enables researchers to explore the relationship between gene expression and clinical traits in AD in comparison to a high-risk population [46]. The use of WGCNA in different studies has been briefly discussed
In a study, using WGCNA, researchers were able to construct and predict co-expression networks of genes implicated in the pathophysiology of AD. WGCNA obtained twenty co-expression modules while the GEO database has been used to download GSE121212[47]. The study aimed to identify significant biomarkers to understand the mechanisms of AD on the molecular level and its treatment. A cluster visualization study was performed by expressing a portion of mRNA and modules, showing that the genes under each module were independent (1000 genes were randomly chosen for display [48]. The WGCNA R package was also utilised in a study[43] to determine hub genes and clinical traits. To rule out samples that weren't normal, the combined gene matrix was examined. Genes were grouped into modules according to their dissimilarity and the adjacency matrix was used to generate the topological overlap matrix (TOM) [49]. The relationship between clinical traits and module Eigen genes were determined using the absolute value of the correlation coefficient between traits and genes. Module genes with AD traits were defined as those having a gene significance (GS) > 0.2 and a module membership (MM) > 0.8 in the most relevant module [50], as shown in Figure 1.

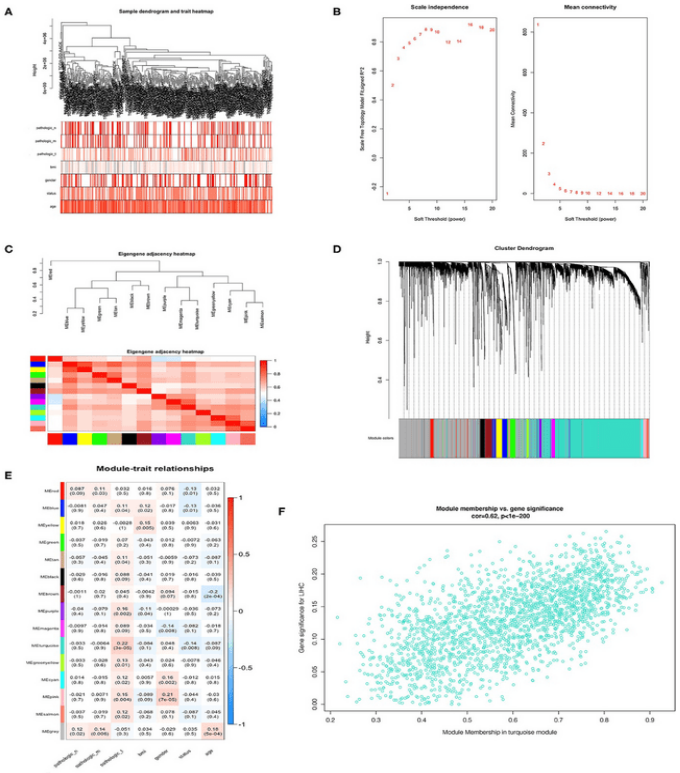

Figure 1. GO Enrichment Analysis[50]

Another study analyzed levels of gene expression having a significant link with the pathogenesis of AD and DEGs [51]. It was necessary to compare AD patients with healthy controls to gain an insight into the variability in biological markers among AD patients. WGCNA was a potential technique for identifying functional subsystems in a population with lower dimensionality transcripts that were physiologically significant[52]. In dataset expression, such as skin and PBMC samples of healthy controls and AD patients, WGCNA has been utilized to identify AD-associated transcriptional modules. The procedure identified 15 transcriptional modules for PBMC (pModus) and 21 transcriptional modules for skin (sModus), each consisting of 51–774 genes that behave synchronously (mean: 258.7 for skin, 191.8 for PBMC)[51], as shown in Figure 2.

Microarray Analysis

DNA microarray is a tool used in research to study DNA simultaneously from different samples or tissues. It provides a range of fabrication techniques, pathways, and frameworks like organized surfaces and labelled beads. This technology is employed for genotyping, assessing gene expression, and quantifying protein profiles in research and clinical environments. DNA microarray technology utilizes densely packed probes that bind to mRNA samples through Watson-Crick base pairing to measure gene activity levels in a particular sample [53]. A study conducted by [54], utilised the microarray technique in canine AD to detect significant changes in the gene expression of lesional nonlesional skin of

AD patients. This technique assesses the amounts of mRNA transcript expression for a vast array of genes in a comparatively small number of case samples and controls [55]. The gene expression in AD patients with lesional skin involved inflammatory changes, while the nonlesional reflects the atopic phenotype. The genes profilarggrin, loricrin, involucrin, S100, and small proline-rich proteins are required for keratinocyte differentiation and the formation of the epidermal barrier [54], as shown in Figure 6.

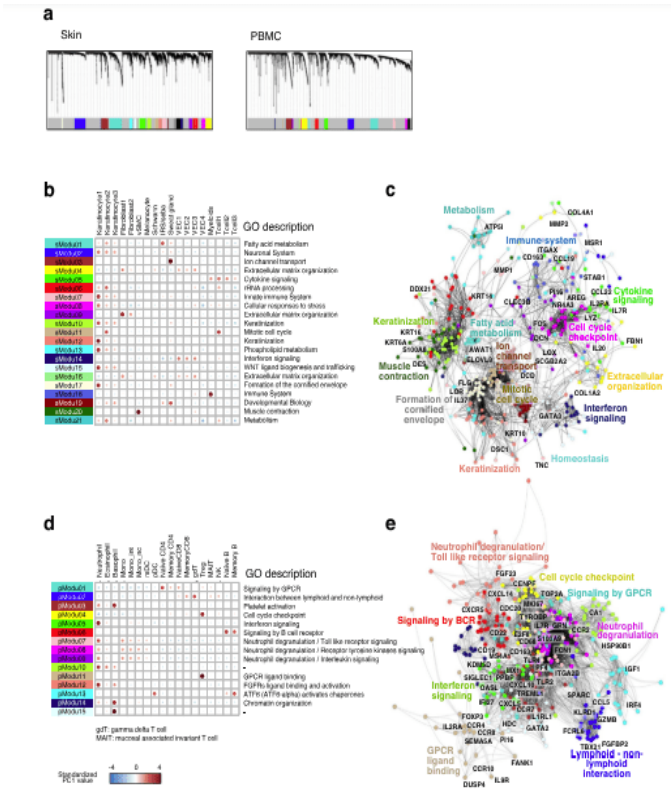

Figure 2. [51]

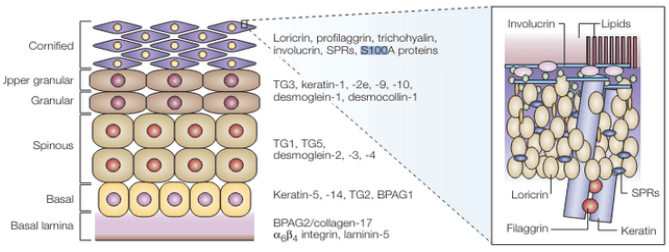

Figure 3 Terminal differentiation and apoptosis in the epidermis [54]

The results of microarray analysis into human AD revealed FLG and loricrin were down-regulated in lesional skin, while S100 was upregulated. Since the creation of the canine array, the results highlighted the significance of FLG in human AD [56].

In a study conducted by [57], as shown in Figure 4, several dysregulated genes and pathways have been identified by microarray and quantitative RT-PCR studies on AD skin specimens, particularly in lesions such as type 2 cytokines and chemokines (IL-13, IL-31, CCL17, CCL18, CCL22, and CCL26), epidermal differentiation and proliferation markers, and TH17/TH22 cell activity-related genes (IL-17A, IL-22, IL-23A/p19, IL-12B/p40, CCL20, DEFB4A, and STAT3) in particular in lesions , as shown in Figure 4.

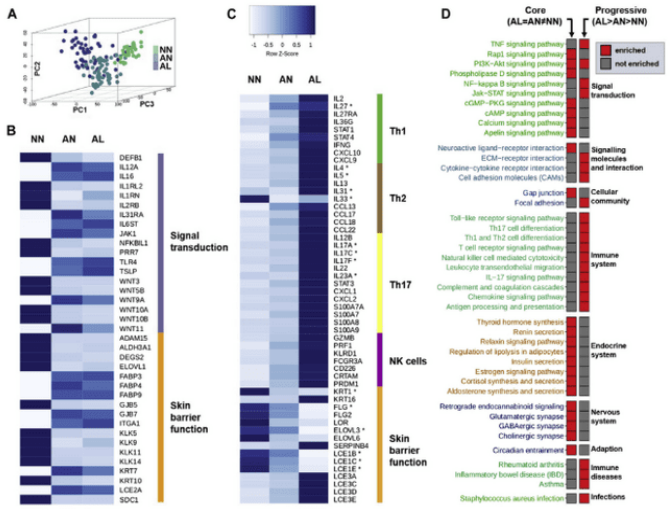

Figure 4. AD skin transcriptome signatures [57]

Planar antigen microarrays, to produce a routine antibody validation workflow has been conducted by [58]. The results of antigen microarray technology revealed the auto-reactivity to S100A12, which was only seen in AD patients. Furthermore, plasma samples from AD patients showed significantly higher levels of increased IgG binding reactivity to three other proteins KRTAP17-1, HSPA4, and S100Z than healthy controls. Additionally, patients with severe AD exhibited a higher frequency of reactivity to these proteins than patients with moderate AD [58].

Evaluating gene ontology and gene-related pathways

Gene Ontology, or OG, is a significant and most commonly used bioinformatics tool. The tool provides a comprehensive analysis of the function of genes of a single genomic product through ontology. The tool comprises three basic items: molecular function, cellular components, and biological processes [59]. Utilization of GO in several different AD studies has been discussed. This study conducted by [43], used DAVID to conduct GO analysis, investigating the pathways and functions of the 328 identified DEGs. According to GO analysis, downregulated genes were primarily involved in skin formation and cell differentiation of epidermis, while upregulated genes were significantly enriched in immune responses within the biological processes category. Furthermore, most upregulated genes were distributed in the extracellular space, whereas the downregulated genes were primarily found in the cellular component analysis. Furthermore, according to the findings of functional molecular analysis, downregulated genes were linked to cell adhesion and molecular binding, whereas upregulated genes were primarily connected to receptor binding, as shown in Figure 5.

Through GO analysis, the mRNA expressions of AD, Allergy-Associated Esophagitis (AA), and Eosinophilic Esophagitis (EoE) were compared [60]. According to the results of GO analysis, common regulatory genes have been frequently involved in the immune system processes of AD, EoE, and AA. The results suggested that in all three diseases, the inflammatory aspect of the diseases was conserved and primarily upregulated. Additionally, GO analysis showed that keratinocyte differentiation-related genes were downregulated in EoE and upregulated in AA [39]. On the other hand, both EoE and AD showed a preferential reduction in the genes

related to epidermal development. Together, these findings suggested that while EoE and AD share some common inflammatory components [61]., there may be differences in the epithelial cell response between the two diseases due to the differential regulation of keratinocyte genes in EoE and AA and the lack of a strong, statistically significant enrichment between EoE and AD [60].

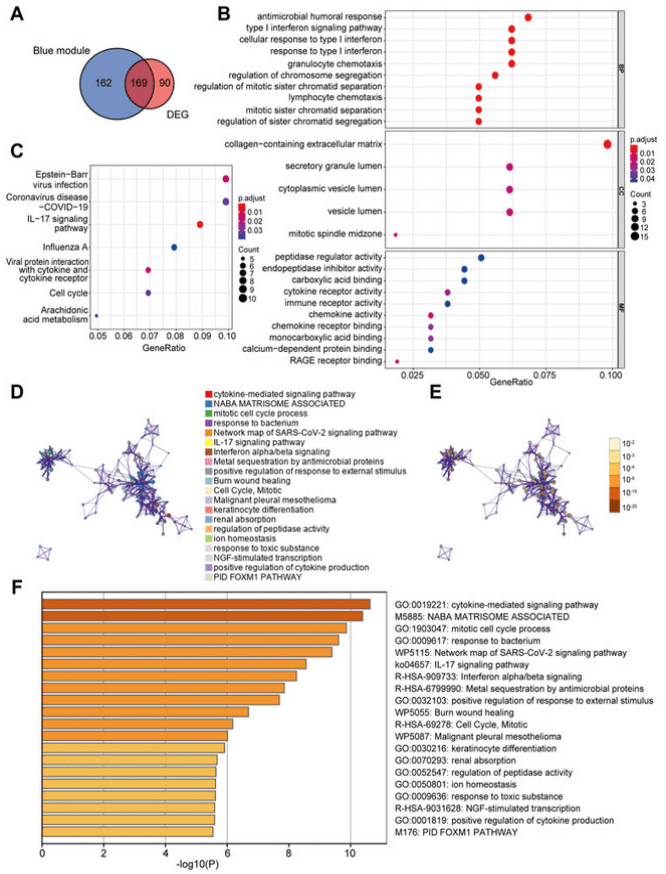

Figure 5 Functional Enrichment Analysis [43]

According to the GO enrichment analysis conducted on AD patients, the commonly reported dysregulation pathway of lipid metabolism is a common feature of psoriasis and is found in AD patients [62]. This feature negatively correlates with the path of immune response. The genes involved in these pathways are normally found in the polyunsaturated fatty acid pathway of PUFA, regulating the proper construction of cell membranes [63]. Gene ontology (GO) has been utilized to describe the gene characteristics and gene products between the datasets and the species with standardization [62]. GO analysis was performed with AmiGO gene ontology version 1.8 to identify the molecular mechanism of GLG in AD pathology. The GO analysis of 127 transcripts revealed a higher association of genes in the extracellular region due to the differential expression of wild-type FLG in AD patients [63].

Analysis of the network and modules of protein-protein interactions (PPI)

Protein–Protein Interactions (PPI) have been a significant tool for examining the protein interaction networks and the identification of several biological activities. This approach helps to identify key proteins that may or may not be involved in the disease or as the part of linking pathway [64]. In another study, conducted by [64], protein interaction analysis was conducted between AD and Tooth Agenesis or TA patients to identify potential markers for research purposes. The PPI analysis found a possible interaction between TA and AD, as shown in Figure 6.

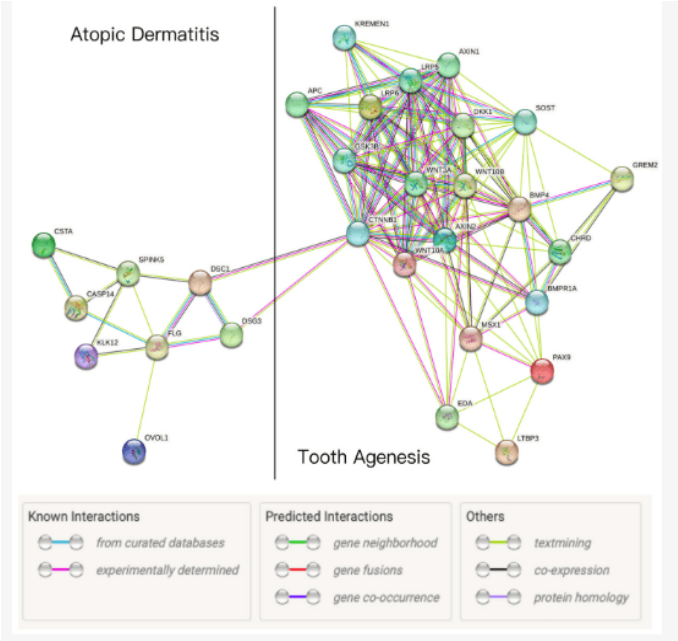

Figure 6. Interaction between TA and AD [64]

Catenin beta-1 (CTNNB1) had a significant interaction with TA and AD-associated AXIN2, WNT10A, WNT10B, and LRP6 genes as an essential downstream element of the Wnt signalling pathway. Additionally, a functional link between desmosomal proteins and CTNNB1, played a significant role in maintaining skin barrier function, regulates AD's pathogenesis[64]. PPI network analysis has also been applied using the STRING database to identify the interactions between DEGs of immune responses in AD, contact dermatitis (CD), and psoriasis (PS). By the analysis in the PPI networks of AD, CD, and PS, the hub genes of AD included CD4, ITGAM, and GRB2; for CD, were CD8A, CD86, ITGB1, and FCGR3A while of PS were CD4, CD8A, GRB2, and ITGB1. Among them, CD2 genes were involved in the pathologies of the disease [65]. The integration of bioinformatics tools like DEG analysis, WGCNA, and PPI networks has significantly enhanced our understanding of AD. These analyses have revealed key genes, pathways, and interactions involved in disease pathogenesis, highlighting potential biomarkers and therapeutic targets. By revealing the molecular mechanisms underlying AD, these studies contribute to the development of personalized medicine approaches and novel treatment strategies. Additionally, utilization of bioinformatics methodologies will be crucial for advancing the knowledge of these complex diseases and applying research discoveries to clinical practice to enhance patient outcomes.

Clinical implications for diagnosis and prognosis

Until December 2016, only calcineurin inhibitors and topical corticosteroids were approved for treating AD. However, long-term use was restricted due to adverse reactions. In 2016, for mild-to-moderate AD, crisaborole 2% ointment was approved, Tralokinumab was invented in 2021 in the European Union and the United Kingdom for moderate-to-severe AD, and dupilumab was approved for moderate-to-severe AD. Janus

kinase inhibitors for moderate to severe AD, such as abrocitinib, baricitinib, and upadacitinib, have been approved worldwide and in Israel since 2022 [66]. A few of them have been discussed below

Dupilumab Treatment

Dupilumab, a monoclonal antibody targeting the IL-4 and IL-13 receptors, is the first biologic approved for treating moderate to severe AD. In a study, phase 3 clinical trials on patients with mild to severe pathogenesis of AD, Dupilomab, with or without the addition of topical corticosteroids, significantly improved disease severity and quality of life for patients until 16 and 52 weeks [67]. For up to 76 weeks, it was shown to be both effective and well-tolerated in the most recent open-label extension study [68]. However, discontinued dupilumab treatment in limited patients (17; 8.1%), with only 8 (3.8%) discontinuing because of adverse effects and 9 (4.3%) because of ineffectiveness [69].

Tralokinumab Treatment

IL-13 is specifically inhibited by tralokinumab. In the ongoing OLE with moderate-to-severe AD in adults, effectiveness of tralokinumab for long-term safety along with optional TCS are examined from earlier parent trials (PT) [70]. In a study, equivalent frequencies of adverse events (AEs) for tralokinumab (65.7%) and placebo (67.2%) were found in Phase II and III studies of safety analysis in adults at W16. SAEs were associated with a higher relative risk of viral upper respiratory tract infections (1.4×), conjunctivitis (2.9×), injection site reaction (12×), and a lower risk of skin infections (0.5×), particularly eczema herpeticum (EH) [71]. Tralokinumab 300 mg Q2W was also approved for use in adolescents in October 2022, according to ECZTRA 6, which demonstrated a similar safety and efficacy profile (28% EASI-75 at W16) to the adult monotherapy studies [72].

Janus Kinase Inhibitor

Janus kinase (JAK) inhibitors represent a promising therapeutic approach for AD by disrupting a broader inflammatory pathway rather than specifically targeting individual cytokines. JAK enzymes are pivotal in the signalling cascade activated by various pro-inflammatory cytokines implicated in AD, such as IL-4, IL-13, IL-22, IFN-γ, and TNF-α [2]. The unique mechanism of action of JAK inhibitors involves blocking specific JAK enzymes, thereby impeding the signalling of multiple cytokines simultaneously. This multifaceted inhibition of the inflammatory pathway provides a distinct advantage over medications exclusively targeting individual cytokines [73].

Challenges and Future Directions

Challenges in AD Research

In the development of AD, understanding the intricate interactions between genetic predisposition, environmental factors, and triggering elements has been a few major challenges in the bioinformatics analysis of the disease. The impact of environmental factors on gene expression has been demonstrated by epigenetic studies, underscoring the necessity of understanding changes in chromatin structure that can either activate or inhibit gene transcription [1, 74]. Additionally, identifying specific and significant biomarkers and immune cell infiltration in AD patient's genome through bioinformatics analysis has been a considerable challenge in understanding inflammatory skin diseases and developing targeted treatments [43, 75]. However, to differentiate cases of pediatric AD from adult cases presents additional difficulties, necessitating the use of particular gene signatures and therapeutic targets for pediatric patients [76]. In addition to the AD treatments that are currently available, significant molecular pathways targeted by several efficient drugs have been introduced to treat the pathology of AD [77]. A few challenges faced in this field were adverse effects by topical steroids and immune suppressant agents due to treatment adherence, trigger avoidance and the economic burden of the treatment due to the high cost of JAK/STAT inhibitors [78]. These more recent biologically small molecules are not one-size-fits-all medications like any other. A variety of factors has been responsible for influencing the response to these drugs, including diverse environmental triggers, complex genotypes, signals derived from the microbiome, and, most importantly, dynamic immune responses, even though the majority of patients are expecting better efficacy and long-term control [79]. It is imperative to combine genomic, epigenomic, transcriptomic, proteomic, and metabolomic methods to understand AD's complexities and develop effective and efficient treatment of the disease [74].

Emerging Technologies in Bioinformatics

Advancements in tools

In recent years, Machine learning (ML) has been significantly applied in several medical fields to improve disease detection and classification, opening a gateway toward personalized treatments [80]. ML-based disease detection has been applied to several data sets, including patient demographic data sets, genomics, and transcriptomics. Artificial intelligence (AI), specifically in the classification of skin diseases, has provided a potentially advantageous strategy to augment diagnostic precision and optimize healthcare operations. [81]. Machine learning techniques can create vector representations of patients, capturing complex patterns and relationships within their electronic health records. These representations can classify patients with AD based on specific criteria. Like BERT models, transformer embedding capture contextual information, improving text data understanding. Machine learning algorithms can classify patients based on their vector representations, enabling automated patient phenotyping. Machine learning models can also assist clinicians in efficient chart review, reducing manual efforts and allowing them to focus on more critical patient care and research [82]. The Derma Care deep learning model has been developed to detect skin diseases like eczema and psoriasis with high accuracy. The model uses a large dataset of skin images, achieving an F1-score of 95.80%, outperforming existing methods. The study emphasizes the importance of early detection and diagnosis of these diseases, which can improve healthcare outcomes and individuals' quality of life. The model can learn about 2 million parameters with reduced computational complexity, making it suitable for mobile phone applications and clinical settings. The model's potential for practical implementation and widespread use in healthcare settings is highlighted, with the model significantly improving the accuracy of skin condition detection, especially for AD-like eczema [83]. Addressing challenges and future directions in

AD research emphasizes the importance of understanding additional epigenetic mechanisms, integrating multi-omics data, formulating personalized treatment strategies based on epigenetic profiles.

Ethical Consideration

Ethical considerations in AD research and treatment involve prioritizing patient well-being, ensuring informed consent, and upholding privacy and confidentiality in handling genetic and clinical data. Researchers must navigate the balance between scientific progress and potential risks to participants, promoting transparency and responsible communication. Ethical considerations need careful attention as the field progress.

Conclusion

The genetic modifications of genes that lead to AD have been linked to immune response alterations, keratinocyte stress response, vitamin D metabolism, and epidermal barrier dysfunction. Bioinformatics techniques like identification of DEGs, WGCNA, Microarray, gene ontology, and PPI networks are crucial for identifying differential gene expression in AD. Future directions in AD research emphasize the need for a comprehensive understanding of epigenetic mechanisms, multi-omics data integration, personalized treatment strategies, and ethical considerations for the advancement in the treatment method of the disease.

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Abbreviations

AD: AD
FLG: Filaggrin
SPINK5: Serine Protease Inhibitor Kazal(-Type 5)
PRRs: Pattern-Recognition Receptors
TLRs: Toll-Like Receptors
NLRs: Nucleotide-Binding Oligomerization Domain-Like Receptors
TSLP: Thymic Stromal Lymphopoietin
FCERIA: Fc Epsilon Receptor I Alpha
IL: Interleukin
VSTM1: V-Set and Transmembrane Domain Containing 1
NLRP2: NLR Family Pyrin Domain Containing 2
TSLP: Thymic Stromal Lymphopoietin
CD4+ T cells: Cluster of Differentiation 4 Positive T cells
CLA+ T cells: Cutaneous Lymphocyte Antigen Positive T cells
VSTM1: V-Set and Transmembrane Domain Containing 1
KIF3A: Kinesin Family Member 3A
HDAC: Histone Deacetylase
miRNA: Micro-RNA
UTR: Untranslated Region
HDAC: Histone Deacetylase
DNMT: DNA Methyltransferase
IL12RB2: Interleukin 12 Receptor Subunit Beta 2
IL-2: Interleukin 2
IL-12: Interleukin 12
IFN-γ: Interferon-gamma
DEGs: Differential Expression Genes
WGCNA: Weighted Gene Co-Expression Network Analysis
GEO: Gene Expression Omnibus
PPI: Protein-Protein Interactions
JAK: Janus Kinase
ML: Machine Learning
AI: Artificial Intelligence
BERT: Bidirectional Encoder Representations from Transformers

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