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Review

Molecular Insights into Acne Vulgaris: A Multi-Omics Approach Towards Precision Medicine

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Abstract. Acne vulgaris is a common dermatological disorder that significantly impacts quality of life, yet its complex pathogenesis remains incompletely understood, contributing to the variability in clinical presentation and treatment response. This review summarizes recent advances in omics-based research on acne vulgaris and explores how these findings support the development of targeted therapy. A systematic literature search was conducted in PubMed using the keywords "acne genomic," "acne transcriptomic," "acne proteomic," and "acne metabolomic." Original research articles published in English, available in full text, and published between 2015 and 2025 were included. After screening for relevance and removing duplicates, 17 studies met the inclusion criteria. Additional relevant articles were also referenced to complement the discussion. The selected studies show that large-scale molecular analysis provides a more comprehensive understanding of the molecular mechanisms underlying acne vulgaris. These findings enable the identification of novel biomarkers, better insight into pathological pathways, and the development of more targeted therapeutic strategies. Further studies are needed to validate these findings and translate them into improved strategies for the diagnosis, prevention, and treatment of acne vulgaris.

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1. Introduction

Acne vulgaris affects more than 85% of adolescents and can persist into adulthood, particularly in women, who account for two-thirds of dermatological consultations for acne. In 2021, acne was around 25% more common in young women than in young men. Although acne is not a life-threatening condition in most cases, if left untreated, it can have serious physical and psychological consequences. Notably, acne is the only dermatological disorder that has been identified as a risk factor for suicide, especially among men [1-2].

The etiology of acne vulgaris involves a complex interplay of genetic, hormonal, environmental, and skin microbiome factors. Despite significant research, the molecular mechanisms underlying acne development remain incompletely understood [3]. Recent advances in omics technologies, an umbrella term for the collection of large-scale biological analyses such as genomics (genes), transcriptomics (gene expression), proteomics (proteins), and metabolomics (metabolites) have provided new opportunities to understand acne pathogenesis. These approaches enable researchers to study the complex interactions among genes, proteins, and metabolites that drive the disease [4].

The large datasets generated by omics studies require sophisticated computational tools, highlighting the essential role of bioinformatics, which translates complex molecular data into clinically meaningful insights [5]. Advances in omics research have also transformed the field of precision medicine, an approach that individualizes disease prevention, diagnosis, and treatment based on each patient's genetic and molecular profile. These tools provide researchers and clinicians with a deeper understanding of disease at the molecular level, enabling the discovery of new biomarkers, better insight into disease pathways, and the development of targeted therapies [6].

Multi-omics in the context of dermatology refers to the integrated use of various omics technologies including genomics (the study of genes and DNA), transcriptomics (the study of gene expression), proteomics (the study of proteins), metabolomics (the study of small molecules and metabolites to gain a comprehensive understanding of the skin and its related conditions. Integrating these data with clinical information helps clinicians design more personalized and effective strategies for diagnosis and treatment [7].

This literature review focuses on the use of multi-omics approach in acne research, beginning with an overview of core omics concepts and methods, followed by their specific applications in acne studies. Ultimately, multi-omics-driven insights pave the way for precision medicine in acne vulgaris by enabling treatment strategies tailored to each individual's molecular profile [8].

2. Experimental Section

A systematic literature search was performed in PubMed to identify studies related to acne vulgaris and multi-omics approaches. The search strategy included the following individual keywords: "acne genomic," "acne transcriptomic," "acne proteomic," and "acne metabolomic." Each keyword was searched separately, and the results were screened for relevance based on titles and abstracts. Only original research articles published in English and available in full text, and published within the last 10 years (2015-2025) were included. After removing duplicates, titles, and abstracts were screened, and only studies that included the terms "acne," "acne vulgaris," or "*Cutibacterium acnes*," and mentioned any omics approach were considered eligible. Finally, only original research articles meeting all inclusion criteria were selected. Ultimately, seventeen studies were selected for this review. To provide a more complete discussion, several additional books and related articles that met the

inclusion criteria and aligned with the purpose of this review were also referenced. Figure 1 shows the flow diagram of the study selection process.

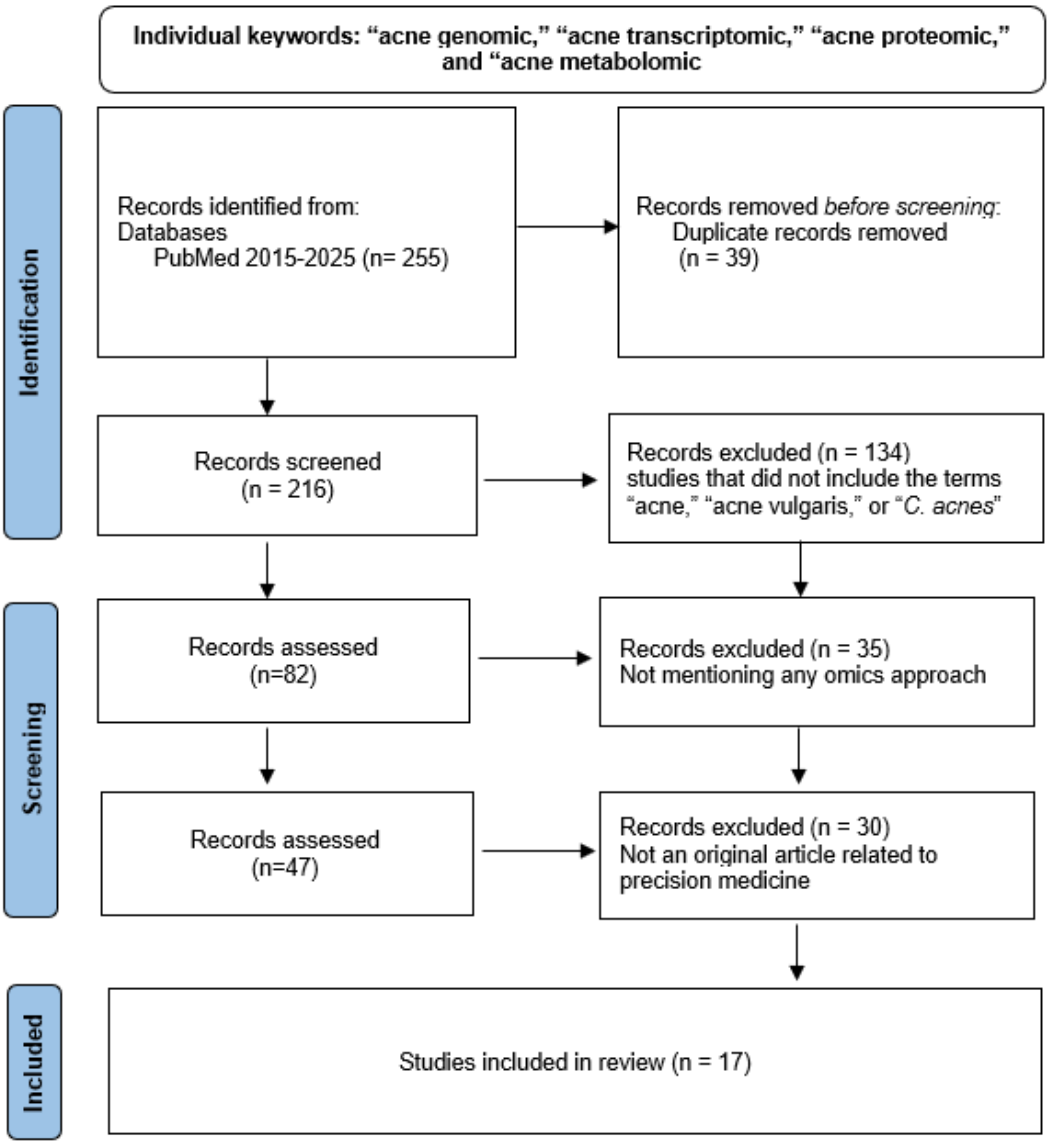

Figure 1. Literature search process

3. Results and Discussion

The pathogenesis of acne vulgaris is multifactorial, involving a complex interplay of hormonal, microbial, immunological, and genetic factors (Figure 2). The multifactorial nature of acne vulgaris contributes to its clinical heterogeneity, thereby posing significant challenges to a comprehensive understanding of its pathogenesis. Acne vulgaris, with its multifactorial pathogenesis and clinical variability, lacks a single deterministic cause, making it unsuitable for single-layer analysis. This nature needs a multi-omic strategy that integrates genomic, proteomic, and metabolomic data to capture the diverse biological processes driving the disease comprehensively [9-10].

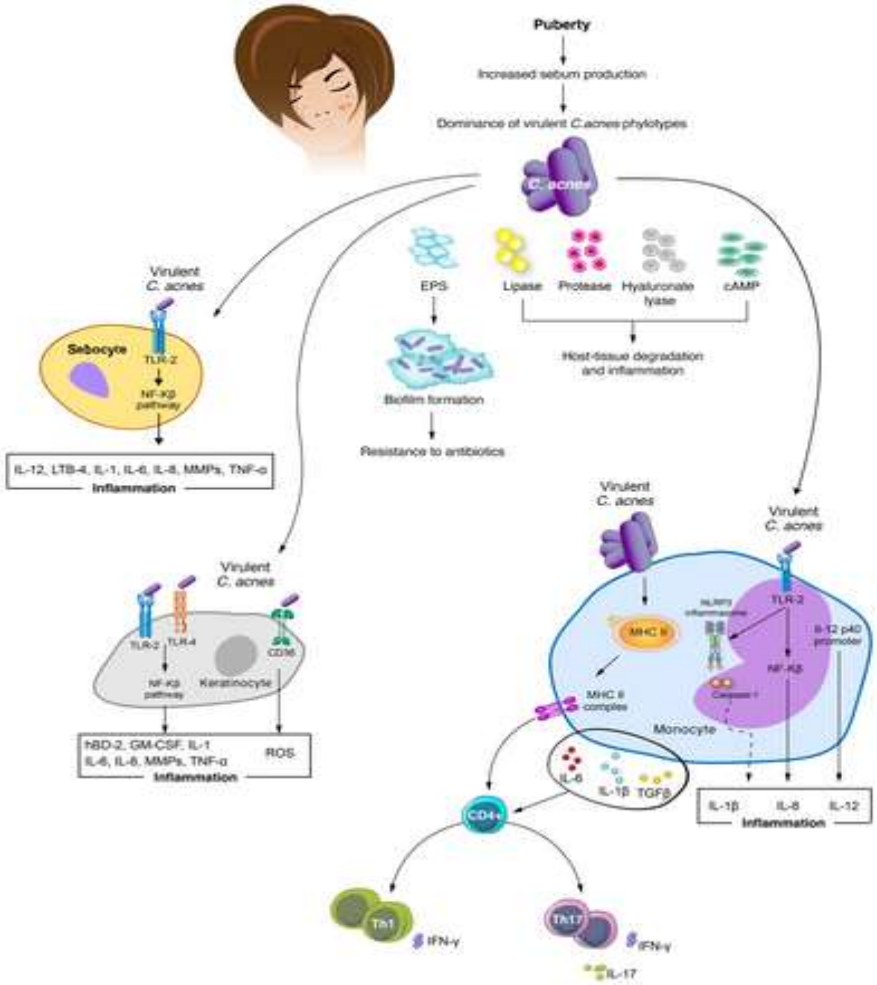

Figure 2. Complex interplay of hormonal, microbial, immunological, and genetic factors in acne vulgaris [10]

3.1 Genomic

Genomics, the earliest of the omics disciplines, focuses on the comprehensive study of an organism's genome to identify genetic variations associated with diseases, treatment responses, and patient prognoses. Epigenomics investigates epigenetic modifications across the genome, such as DNA methylation, histone modifications, chromatin remodeling, and nuclear organization that regulate gene expression without altering the DNA sequence. These modifications influence cellular phenotype and can be passed down through generations [11].

Genomic research utilizes high-throughput sequencing technologies, sequence assembly, and genome annotation. The evolution of genomic technology began with DNA microarrays, followed by first-generation sequencing using the Sanger method. This was later succeeded by second-generation sequencing, commonly known as Next-Generation Sequencing (NGS), and eventually, third-generation sequencing, which allows for the reading of longer DNA sequences. Key genomic techniques like include Genome-Wide Association Studies (GWAS), Expression Quantitative Trait Loci (eQTL) Analysis, Whole Exome Sequencing, Whole Genome Sequencing (WGS), and Targeted Sequencing enable detailed mapping of genetic variations, offering insights previously unattainable [11]. These genomic techniques have provided new opportunities to explore the molecular

mechanisms underlying acne vulgaris. Here we summarize key findings from recent genomic studies on acne vulgaris.

Table 1. Key Findings from Genomic Studies on Acne

No	Article title	Key Finding
1	Genome-wide association meta-analysis identifies 29 new acne susceptibility loci [12]	29 new genetic loci linked to acne were found, increasing the total known risk loci to 46. Key genes were involved in hair follicle structure, cell adhesion, and inflammation. Based on the genetic risk score calculated from the 46 acne-associated loci, it was predicted that genetic factors contribute approximately 5.6% to an individual's risk of developing acne.
2	Whole genome sequencing distinguishes skin colonizing from infection-associated *Cutibacterium acnes* isolates [13]	Genomic differences between harmless and infection-associated *C. acnes* strains are found in genes related to metabolism and DNA repair, not in traditional virulence genes. This suggests that *C. acnes* ability to cause infection may depend more on its metabolic adaptability than on known virulence factors.
3	Analysis of intracellular communication reveals consistent gene changes associated with early-stage acne skin [14]	There are changes in 49 signaling pathways in lesional skin compared to healthy skin, with 10 genes (including GRN, IL-13RA1, and SDC1) consistently dysregulated across all patients.
4	Identity-by-Descent Analysis Reveals Susceptibility Loci for Severe Acne in Chinese Han Cohort [15]	Identification of two new genetic loci (F13A1 and ADH7) linked to severe acne, along with validation of a previously known locus (DDB2). This reveals ethnic-specific genetic factors and highlights inflammation-related pathways, improving understanding of severe acne genetics in Chinese Han population

A genome-wide meta-analysis discovered 29 additional loci, raising the total number of acne-associated loci to 46. A polygenic risk score based on these loci accounted for up to 5.6% of acne risk, highlighting their potential for use in risk stratification [12]. Other genomic studies have also identified numerous risk loci for acne, with limited predictive power and only explaining a small fraction of the total risk [16]. These findings may not fully account for environmental interactions or population-specific genetic variation.

In parallel, another analysis of lesional skin found consistent dysregulation of inflammation-related genes (*GRN*, *IL13RA1*, *SDC1*), linking genetic susceptibility to active disease mechanisms and suggesting these genes as therapeutic targets. [14] Additionally, a GWAS in the Chinese Han population identified two novel loci (*F13A1* and *ADH7*) related to severe acne, emphasizing the importance of population-specific targets in personalized therapy [15].Altogether, these findings show that genomics can guide both early risk prediction and targeted treatment strategies for acne. Their integration into clinical practice holds strong potential to advance precision medicine in dermatology, enabling more individualized approaches to acne management based on a person's genetic profile, disease severity, and ethnic background.

From the microbial side, genomic comparisons of *C. acnes* strains revealed that differences between skin-colonizing and disease-causing lineages lie not in classical virulence genes, but in genes involved in metabolism and DNA repair [13]. Similar research emphasizes metabolic adaptations

specific to acne-associated strains and reveals how strain-level differences in metabolism, rather than classical virulence traits alone, contribute to pathogenicity in acne vulgaris [17].

3.2 Transcriptomic

Transcriptomics examines the transcriptome, which includes all RNA molecules transcribed from the genome under specific conditions. This field provides a snapshot of gene expression at a particular moment. However, transcription levels do not always directly correspond to protein expression due to post-transcriptional modifications [18]. Various techniques are employed in transcriptomics, including Serial/Cap Analysis of Gene Expression (SAGE/CAGE), Expressed Sequence Tag (EST), Suppression Subtractive Hybridization (SSH), microarrays, and RNA sequencing (RNA-Seq). These methods enable the measurement of gene expression across different cell populations, which can be influenced by treatments, diseases, or environmental factors at different time points.

Microarrays remain a widely used technology due to their cost-effectiveness, high-throughput capability, and well-established platforms. RNA-Seq has emerged as a significant innovation in transcriptomics, integrating advanced deep-sequencing technologies with computational approaches for simultaneous transcriptome mapping and quantification [18]. Leveraging these transcriptomic tools, researchers have begun to unravel gene expression changes associated with acne vulgaris. The following table summarizes key findings from recent studies.

Table 2. Key Findings from Transcriptomic Studies on Acne

No.	Article title	Key Finding
1	Identification of biomarkers of acne based on transcriptome analysis and combined with network pharmacology to explore the therapeutic mechanism of Jinhuang ointment [19]	Acne-related biomarkers such as IL-1β, CXCL8, TLR2, CXCL2, LCN2, and SPP1 were identified and verified. There is stable binding activity between the main active components of JHO and therapeutic targets (CXCL8, ESR1, IL-1β, MMP1, MMP3, and SPP1). CXCL8, IL-1β, and SPP1 are not only potential acne biomarkers but also primary targets of JHO.
2	Transcriptomic Analyses Predict Enhanced Metabolic Activity and Therapeutic Potential of mTOR Inhibitors in Acne-Prone Skin [20]	A total of 77 genes were found to be differentially expressed in acne-prone skin without lesions (NLA), including genes related to innate immunity and epidermal barrier function. Some genes, such as KRT6C, KRT16, S100A8, and S100A9, showed an increase, while LCE4A, LCE6A, and CTSE showed a decrease. Pathway analysis revealed increased metabolism in NLA skin and reduced keratinization. Through connectivity mapping, 187 compounds, including mTOR inhibitors, were identified as potential agents to modulate gene expression in acne-prone skin.
3	Integration of Single-Cell Transcriptomics Data Reveal Differences in Cell Composition and Communication in Acne [21]	Acne lesions show increased basal cells and macrophages, with stronger cell communication involving endothelial cells. Males have more macrophages and inflammation, while females have more basal cells and distinct immune signals. These cells are key in acne and potential targets for personalized treatments.
4	Identification of differentially methylated genes for severe acne by genome-wide DNA methylation and gene expression analysis [22]	Inflammatory genes, particularly TNF-α, are upregulated in patients with severe acne. Specific genetic variants in the TNF-α promoter region (□ 863 G > A and □ 308 G > A) are associated with increased TNF-α expression and elevated serum levels. These patients also show higher insulin resistance, indicating a potential connection between inflammation and metabolic dysfunction in severe acne.

The reviewed studies collectively reveal that acne pathogenesis is a multifactorial process involving complex molecular, cellular, and systemic interactions. Consistently, inflammatory biomarkers such as IL-1β, CXCL8, and SPP1 emerge as crucial elements linked to acne development and serve as promising therapeutic targets [19]. Gene expression analyses in acne-prone but non-lesional skin indicate early dysregulation in innate immunity and epidermal barrier function, highlighting opportunities for preventive strategies before lesion onset [20].

At the cellular level, acne lesions demonstrate altered composition, including increased basal cells and macrophages, alongside enhanced intercellular communication involving endothelial cells. Notably, gender differences influence cellular abundance and immune signaling, suggesting that personalized treatment approaches could improve clinical outcomes [21]. Furthermore, in severe acne, elevated expression of inflammatory genes like TNF-α, associated with specific genetic promoter variants, correlates with increased inflammation and metabolic alterations such as insulin resistance [22].

Taken together, these observations highlight precision medicine in acne management and how individual variabilities such as immune dysregulation in early-onset disease, cell composition changes, sex-specific responses of the immune network, and functional single-nucleotide polymorphisms linked to inflammation and metabolism contribute towards disease onset, severity, and response to treatment. Understanding these molecular and cellular differences allows for the development of personalized treatments that address the specific biological processes driving acne in each individual.

3.3 Proteomic

Proteomics involves identifying and quantifying all proteins within a cell or tissue, offering crucial insights into protein function in both normal and diseased conditions. It also provides information on the spatial and temporal distribution of proteins in cellular components, which is vital for understanding disease mechanisms beyond genomic data alone. Proteomics research uses techniques like mass spectrometry, affinity proteomics, protein chips, and reverse-phased protein microarrays to study proteins on a large scale. In medicine, it is valuable for biomarker discovery, drug target identification, and understanding cellular pathways, contributing to precision medicine [23].

Proteomics begins with protein extraction, purification, and digestion, followed by analysis using tandem mass spectrometry (MS/MS). The spectral data is processed to identify and quantify proteins by comparing them with databases [24]. Post-analysis, bioinformatics tools like GO, KEGG, and STRING help interpret protein functions, pathways, and interactions. Statistical analysis and visualization further reveal key protein expression patterns, offering insights into cellular functions and disease mechanisms [25].

Using a proteomic approach, recent studies in acne vulgaris have advanced our understanding of protein-level changes involved in its pathogenesis. The following table summarizes key findings from several proteomic studies related to acne.

Table 3. Key Findings from Proteomic Studies on Acne

No	Article title	Key Finding
1	Different *Propionibacterium acnes* Phylotypes Induce Distinct Immune Responses and Express Unique Surface and Secreted Proteomes [26].	The *P. acnes* phylotype associated with acne induces IFN-γ and IL-17 levels up to three times higher in peripheral blood mononuclear cells compared to phylotypes associated with healthy skin. Conversely, the *P. acnes* phylotype associated with healthy skin induces IL-10 levels up to four times higher. Adhesion proteins are expressed at least ten times higher in the phylotype associated with acne. Surface hydrolases are expressed in all phylotypes except those associated with healthy skin.
2	Comparative Proteomic Analysis of Membrane Vesicles from Clinical *C. acnes* Isolates with Differential Antibiotic Resistance [27]	Membran vesicles from antibiotic-resistant *C. acnes* strains showed significantly higher levels of two lipases and the cell division protein FtsZ ($p < 0.05$). Improper antibiotic use may drive resistance, disrupt skin lipid composition, and increase inflammation, worsening acne. The study highlights the need for prudent antibiotic use and suggests FtsZ as a potential therapeutic target against multidrug-resistant *C. acnes*.
3	Identification of Novel Protein Biomarkers and Drug Targets for Acne Vulgaris by Integrating Human Plasma Proteome with Genome-Wide Association Data [28]	Nineteen plasma proteins were linked to acne risk, with FSTL1 and ANXA5 showing strong causal associations, elevating acne risk by 24% and 32%, respectively. TIMP4 also emerged as a significant protein influencing acne risk and a potential therapeutic target.

Protein-level changes play a multifaceted role in acne pathogenesis, as shown by diverse proteomic investigations (Table 3). Proteomic alterations contribute to both microbial virulence and inflammation [26]. Acne-related phylotype induces more inflammation and expresses higher adhesion proteins. Improper use of antibiotics can even worsen acne by promoting resistance, disrupting skin lipid homeostasis, and triggering inflammation [27]. Proteomics is a powerful tool not only for understanding disease mechanisms but also for identifying potential biomarkers for potential therapeutic targets. Some protein serves as potential therapeutic targets for acne [28].

Proteomics offers a deeper understanding of how proteins interact, change, and function in both healthy and acne-affected skin than genetics alone can. However, protein research is not without challenges. Because of their complex structures, wide concentration ranges, and need for specific analysis methods and tools, the procedure could be difficult [29]. Even when the experiments are done properly, one of the biggest challenges in proteomics is the incompleteness of current protein databases. This will limit the ability to fully identify all proteins present in a sample [30]. Despite proteomics limitations, proteomics has the potential to uncover the mechanisms behind acne and pave the way for more specialized, customized dermatological treatments.

3.4 Metabolomic

Disruptions in biological systems can lead to complex metabolic changes, making metabolites valuable indicators of an organism's phenotype. Metabolomics, a field within systems biology, examines metabolic products in cells, tissues, organs, or entire organisms under specific conditions. By examining metabolic pathways, this field helps elucidate how metabolites interact and how they are influenced by genetic changes, environmental factors, or diseases [31].

Metabolomics utilizes various analytical techniques, including Nuclear Magnetic Resonance spectroscopy, Fourier transform infrared spectroscopy, GC-MS, LC-MS, and capillary electrophoresis-MS. Two primary approaches are employed: unsupervised analysis, which identifies all metabolites in a sample, including unknown compounds, making it ideal for exploratory research and biomarker discovery, and supervised analysis, which focuses on detecting known metabolites by comparing them with reference databases containing spectral data, nomenclature, concentrations, biological locations, and enzyme-related information. [32] NMR spectroscopy is widely used due to its non-destructive nature and ability to analyze multiple compounds simultaneously, while MS techniques offer higher sensitivity, for the detection of low-concentration metabolites across a broad range of polarities.[33]

As one of the most recent omics approaches, metabolomics has gained increasing attention and has been applied to explore complex skin conditions such as acne vulgaris. The summary of key findings from recent metabolomic studies on acne vulgaris can be seen below.

Table 4. Key Findings from Metabolomic Studies on Acne

No	Article title	Key Finding
1	Integrated targeted serum metabolomic profile and its association with gender, age, disease severity, and pattern identification in acne [34]	There are significant differences in the metabolomic profile between acne subjects and healthy controls, as well as among subgroups based on gender, age, disease severity, and pattern identification. Acne patients have lower levels of essential amino acids (EAA) and non-essential amino acids (NEAA) compared to healthy controls. In female acne patients, DHEA-S and free fatty acid (FFA) levels are higher than in males. Additionally, the Phlegm-stasis group has higher levels of interleukin (IL)-1β and IL-6 compared to the control group.
2	Untargeted metabolomics analysis of the plasma metabolic signature of moderate-to-severe acne [35]	Significant metabolic changes occur in patients with moderate to severe acne. 56 metabolites show an increase (fold change >1), and 7 metabolites show a decrease (fold change <1). The highest increase is in 2-Oxoadipic acid, while the greatest reduction is in myoinositol. The most affected metabolic pathways include ATP-binding cassette (ABC) transporters and the sphingolipid signaling pathway.
3	Lipidomics of facial sebum in the comparison between acne and non-acne adolescents with dark skin [36]	Adolescents with acne have significantly higher sebum excretion rates on both the forehead and cheeks compared to controls without acne. Acne sebum shows significant lipid alterations, with increased levels of triglycerides, squalene, MUFAs, and odd-chain SFAs, along with reduced fatty alcohols and anteiso-branched fatty acids. Notably, squalene levels correlated with comedone count, linking lipid composition to acne severity. Differences in sebum lipid profiles were more pronounced on cheeks than foreheads in acne patients

Serum and plasma metabolomic profiles reveal substantial differences between individuals with acne and healthy controls [34-35]. These differences are also observed across subgroups based on severity. Furthermore, a previous study shows differences in the metabolomic profile between female and male patients [34]. This suggests that gender may influence metabolic pathways involved in acne pathogenesis. Another metabolomic study in adolescents with acne shows different lipid profiles based on facial location [36]. These location-dependent variations indicate that lipid imbalance may differ across facial regions and play distinct roles in the progression of acne.

3.5 Role and Challenges of Omics Data Integration in Precision Medicine for Acne Vulgaris

As research complexity increases, studying a single omics aspect alone is no longer sufficient to meet the growing demands of scientific investigations. Therefore, integrating various omics approaches has become essential. Proper integration and in-depth scientific analysis will be more beneficial in systematically and comprehensively uncovering the etiology and pathogenesis of acne vulgaris. This multi-omics approach is expected to make significant contributions in various aspects, including providing more valuable research data for skin disease diagnosis, predicting disease progression, and discovering new biomarkers [8], [37].

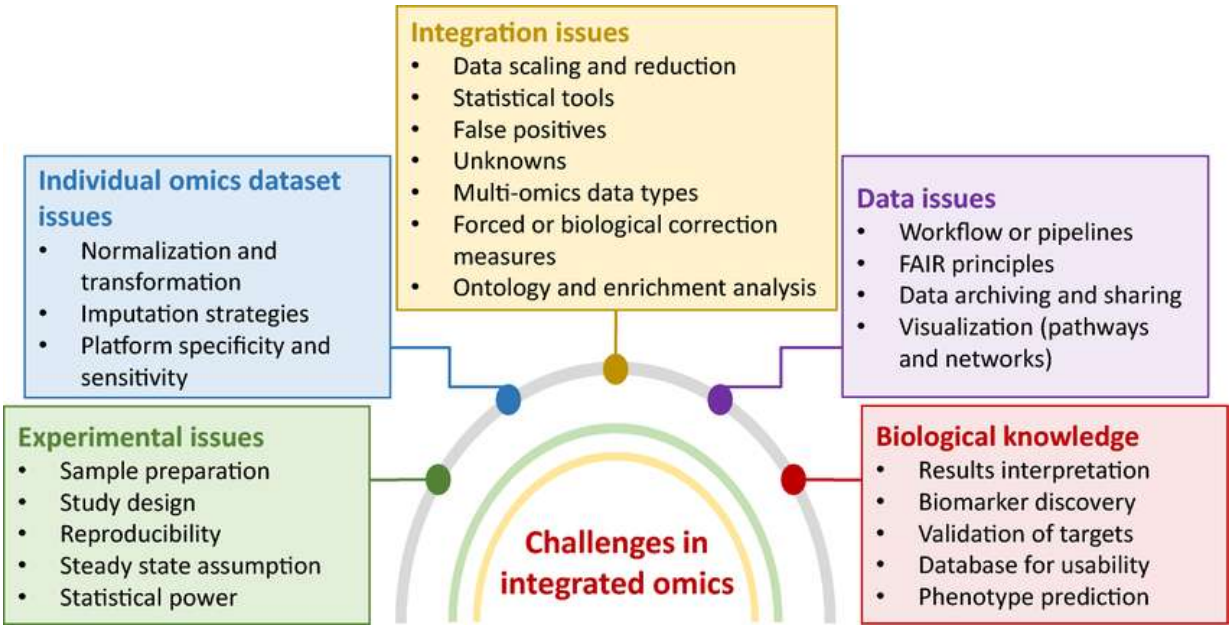

Figure 3. Challenge in integrated omics [38]

Advance in biotechnology have enabled the analysis of both single and multi-omics, along with the integration of multi-omics data, which offers a comprehensive view of disease pathophysiology. Omics data provides highly detailed insights into an individual's biological characteristics, including genetic information, gene expression, protein profiles, and metabolism. The comprehensive overview derived from omics data facilitates the realization of precision medicine. By integrating omics data into clinical practice, clinicians can establish criteria for patient classification and develop models to identify and classify clinical decisions for each disease phenotype [38-39].

High-throughput omics technologies have revolutionized biological research by enabling large-scale data generation; however, they present major challenges in data integration and interpretation due to their complexity, heterogeneity, and lack of standardization. At the individual omics dataset level, issues such as normalization and transformation, imputation strategies for missing values, and platform specificity and sensitivity can significantly influence downstream analyses. Experimental design also plays a critical role, with factors including sample preparation, reproducibility, steady-state assumptions, and statistical power directly affecting data quality and interpretability. When combining datasets, it's important to adjust them to the same scale, choose the right analysis methods, reduce errors, and handle unknown factors. Because the data come from different sources, they often need specific corrections, and pathway or function analyses must be done carefully to avoid wrong conclusions. This careful approach is key in precision medicine, where strong multi-omics integration

helps find reliable biomarkers, assess each person's health risks, and design treatments that fit the individual [40].

Nonetheless, limited bioinformatics training remains a key bottleneck for many researchers. Despite these hurdles, multi-omics integration offers transformative potential in identifying biomarkers, understanding complex diseases, and advancing personalized medicine. Emerging technologies like cloud computing and big data analytics further support the storage, analysis, and sharing of large-scale omics data, paving the way for more comprehensive molecular atlases and predictive models in precision medicine [41-42].

To maximize the utility of integrated datasets, strong workflows, compliance with FAIR (Findable, Accessible, Interoperable and Reusable) principles, proper data storage and sharing, and advanced visualization are essential. Turning multi-omics data into useful biological insights also needs careful interpretation, biomarker validation, solid databases, and accurate phenotype prediction. These steps are vital for precision medicine, as they ensure that complex data can be translated into personalized diagnoses, risk assessments, and targeted treatments for acne vulgaris [40].

4. Conclusion

In the era of precision medicine, omics data plays a crucial role in supporting disease diagnosis, prognosis, and treatment customization. Genomic data enable the identification of genetic variants and susceptibility loci, providing early insights into disease risk. Transcriptomics reveals dynamic gene expression changes that reflect disease progression and immune responses. Proteomics contributes to the discovery of differentially expressed proteins that may serve as diagnostic or prognostic biomarkers. Metabolomics uncovers altered metabolic signatures linked to inflammation and microbial interaction. Multi-omics integration in acne vulgaris allows researchers to uncover complex molecular pathways and identify disease subtypes, enabling more precise diagnostics and personalized therapies. This approach represents a key step toward precision medicine by tailoring treatment to individual molecular profiles for improved clinical outcomes.

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