Advances in Multi-omics Research on IgA Vasculitis (Postprint)

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Abstract

IgA vasculitis is a common systemic small-vessel vasculitis in childhood, characterized primarily by the deposition of IgA immune complexes. It manifests as cutaneous purpura with or without gastrointestinal injury, joint damage, and renal involvement. Long-term prognosis is mainly associated with the severity of renal damage, with some patients progressing to end-stage renal disease, thereby jeopardizing children' s physical and mental health. The etiology, pathogenesis, and progression mechanisms of IgA vasculitis are complex and remain inconclusive to date. Omics technologies, as effective tools for disease research, have been gradually applied to identify biomarkers at different molecular levels and to explore mechanisms of pathogenesis and progression in IgA vasculitis, yielding certain results. By reviewing the current literature on omics studies in IgA vasculitis, this article summarizes and analyzes the application status and progress of various omics technologies in IgA vasculitis, aiming to provide ideas and directions for future in-depth research.

Full Text

Multi-omics Research Progress of IgA Vasculitis

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Abstract

IgA vasculitis (IgAV) is a common systemic small-vessel vasculitis in childhood, characterized by IgA-dominant immune complex deposition in blood vessel walls, manifesting as skin purpura with or without gastrointestinal, joint, and renal involvement. Long-term prognosis is primarily determined by the severity of renal damage, with some patients progressing to end-stage renal disease, posing significant threats to children' s physical and mental health. The etiology and pathogenesis of IgAV remain complex and poorly understood. As an effective tool for disease research, omics technologies have been gradually applied to identify biomarkers at different molecular levels and explore pathogenic mechanisms in IgAV, yielding promising results. This review summarizes current literature on IgAV omics studies, analyzing the application status and progress of various omics technologies in IgAV to provide insights and directions for future research.

Keywords: IgA vasculitis; IgA vasculitis nephritis; Multi-omics; Genomics; Transcriptomics; Proteomics; Metabolomics

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1. Literature Search Strategy

We searched PubMed, CNKI, Wanfang Data, and VIP Information databases from inception to December 2024. Chinese search terms included "IgA vasculitis," "Henoch-Schönlein purpura," "IgA vasculitis nephritis," "Henoch-Schönlein purpura nephritis," and "omics." English search terms included "IgA Vasculitis," "Henoch-Schönlein purpura," "IgA vasculitis nephritis," "Henoch-Schönlein purpura nephritis," "Omics," "Genomics," "Epigenomics," "Transcriptomics," "Proteomics," "Metabolomics," "Multiomics," and "Microbiomics." Inclusion criteria were studies involving omics research on IgAV. Exclusion criteria included irrelevant topics, flawed study design, poor quality, and duplicate publications.

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2. Genomics Research

Genomics investigates genome structure, function, variation, and their effects on organisms to explore relationships between genetic variation and disease occurrence [20]. Current understanding suggests IgAV develops in genetically susceptible individuals under environmental influences that trigger immune dysfunction [11]. Genomic approaches help identify susceptibility genes and molecular genetic information in IgAV.

2.1 Genome-Wide Association Study (GWAS)-Based Genomics

GWAS identifies disease-associated sequence variants across the genome by collecting DNA and phenotypic data, and has been widely used to discover susceptibility genes for complex diseases [21]. LÓPEZ-MEJÍAS et al. [22] reported in a Spanish cohort that IgAV is associated with HLA Class II

polymorphisms. Subsequently, XIA Liang et al. [23-24] identified HLA-DRB1 alleles and amino acid variants within the major histocompatibility complex region as associated with IgAV susceptibility in Chinese Han populations. KOSKELA et al. [25] further investigated genes related to renal injury in IgAV, conducting GWAS and HLA allele imputation on 44 Finnish pediatric IgAVN samples. Their results indicated that HLA-DQA1, DQB1, and DRB1 haplotypes were associated with IgAVN susceptibility but not with renal involvement severity. Using 49 inflammatory bowel disease GWAS studies as controls, they confirmed these loci as specific markers for IgAV, independent of general autoimmune disease susceptibility.

These studies provide valuable insights for identifying key genetic markers, assessing individual susceptibility, predicting renal involvement, and distinguishing similar diseases, offering important guidance for future investigations into how genetic factors influence IgAV susceptibility and severity. However, to date, only 12 GWAS have been conducted on IgAV [25], and genes associated with susceptibility and renal damage require further exploration.

2.2 Whole Exome Sequencing (WES)-Based Genomics Exons are coding regions of the genome that transcribe mature RNA, encompassing approximately 85% of known pathogenic gene variants [26]. WES sequences DNA in exonic regions to identify coding region genetic variants associated with IgAV [27]. JIN et al. [28] used family samples to identify pathogenic genes for IgAV, discovering MIF and MGAT5 as potential new susceptibility loci through WES of three DNA samples from one IgAV family. LI Qiying [29] explored different gene expression profiles across TCM syndrome types in IgAVN patients using WES, performing differential analysis on six IgAVN patients with heat-toxin injuring collaterals syndrome versus healthy children to screen for pathogenic mutation genes, ultimately identifying COL4A3 and COL4A4 as potential pathogenic genes for this syndrome, providing a new breakthrough for modernized TCM diagnosis. However, large-sample validation is still lacking. While WES technology for pathogenic gene identification is mature and offers advantages of high accuracy, efficiency, and low cost compared to GWAS, its application in IgAV remains relatively limited.

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3. Epigenomics Research

Epigenomics documents chemical modifications to DNA and histones, including chromatin remodeling, DNA methylation/demethylation, and histone acetylation/methylation. These modifications can be transmitted to daughter cells, finely regulating gene expression without altering DNA sequences and are dynamically influenced by environmental factors [30]. Epigenomics research on IgAV remains in early stages, with only isolated studies on histone modifications and DNA methylation related to TCM syndrome types.

LUO Shuangyan et al. [31] found differences in overall histone acetylation and methylation levels in peripheral blood mononuclear cells between IgAV patients and healthy individuals, suggesting IgAV pathogenesis may involve abnormal epigenomic changes resulting from altered histone modifications. CAI Mingyang et al. [32] used DNA methylation to investigate differences between TCM syndrome types, identifying NOTCH1, SMAD3, and MALT1 as differentially methylated genes between wind-heat injuring collaterals syndrome and blood-heat reckless movement syndrome. However, the small sample size was insufficient to clarify the relationship between these methylation changes and syndrome differences.

The same team further elucidated the mechanisms of TCM empirical formulas "Liangxue Tuizi Fang" and "Qufeng Xiaodian Fang" in treating blood-heat reckless movement syndrome and wind-heat injuring collaterals syndrome, respectively, finding that IgAV pathogenesis involves primarily DNA demethylation changes. Liangxue Tuizi Fang may exert therapeutic effects by regulating methylation of STAT3 and CD4 genes, while Qufeng Xiaodian Fang may treat wind-heat injuring collaterals syndrome by modulating FOXO signaling pathways and IL7R gene expression, thereby dual-regulating abnormal methylation states [33-34]. Currently, IgAV epigenomics research is insufficient to clarify the intrinsic mechanisms of epigenetic modifications in IgAV pathogenesis, progression, and treatment [35].

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4. Transcriptomics Research

Transcriptomics investigates gene expression at the RNA level [36]. Researchers have gradually explored specific RNA expression in IgAV and IgAVN pathogenesis and progression, focusing primarily on microRNA (miRNA) as potential novel biomarkers for diagnosis, monitoring, and disease severity assessment [37].

LI Gen et al. [38] found elevated miR-155 expression in peripheral blood of IgAV children, which may affect IgAV development by influencing Th17/Treg balance. MA Jinzhao et al. [39] reported low miR-146a expression in adult IgAV patients, promoting inflammation mediated by c-Jun N-terminal kinase (JNK) expression and providing a basis for IgAV diagnosis and treatment. WANG Xiaoli et al. [40] found low serum miR-145 levels and Th1/Th2 ratios in IgAV children, with positive correlation between them, suggesting they may mutually influence IgAV pathogenesis.

YU Shaofei et al. [41] discovered that miR-218-5p may participate in IgAV and IgAVN pathogenesis and progression by targeting high mobility group protein B1 (HMGB1) expression, representing a potential therapeutic target. ZHANG Xinbo et al. [42] found significantly higher miR-221 expression in peripheral blood B lymphocytes of IgAVN patients compared to IgAV patients, suggesting predictive value for renal injury. FAN Li et al. [43] reported low miR-34b expression in IgAVN pathological tissues, which may aggravate lesions by promoting

IL-6-mediated inflammatory cascades. However, these studies are mostly small-sample, single-center explorations with potential biases.

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5. Proteomics Research

Proteomics systematically analyzes protein differences in biological systems (cells, tissues, organs, or organisms) to understand physiological and pathological changes, screen biomarkers, and analyze pathogenic mechanisms [44]. Recent studies have quantitatively analyzed proteomic changes in IgAV patient body fluids (blood, urine) to identify differential proteins between IgAV, IgAVN, and healthy individuals, as well as among different TCM syndrome types. These studies have revealed that complement components, angiotensin, apolipoproteins, and other differential proteins participate in IgAV pathogenesis and renal injury, with distinct proteins across syndrome types, providing references for further IgAV research through enriched biological pathways [45-54] (Table 1).

HE Xuelian et al. [45] identified differentially expressed proteins in serum among IgAV, IgAVN, and healthy groups related to hemostasis and Wnt signaling pathways, validating angiotensinogen as a potential marker for IgAV progression. FANG et al. [50] used data-independent acquisition (DIA) mode with liquid chromatography-tandem mass spectrometry to identify 125 differentially expressed proteins in urine from IgAVN and healthy children, with 41 proteins showing direct interactions involved in focal adhesion, cell adhesion molecules, PI3K-Akt signaling, and ECM-receptor interactions. They further validated tenascin as a marker for early renal injury in IgAVN children. These proteomics studies provide technical support for investigating IgAV pathogenesis and screening specific biomarkers, but face limitations including small sample sizes, limited sample type diversity, lack of specificity in candidate protein biomarkers requiring large-scale clinical validation, non-standardized detection workflows, and substantial differences in quality control standards.

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6. Metabolomics Research

Metabolomics investigates changes in endogenous metabolic networks and relationships among metabolites following internal or external stimuli [55]. Metabolomic studies have revealed significant alterations in serum and urine metabolic profiles of IgAV patients, with distinct metabolic characteristics among different TCM syndrome types involving multiple dysregulated metabolic pathways (Table 2).

REN Xianqing et al. [56] identified eight differential metabolites (including lipids and amino acids) between wind-heat injuring collaterals syndrome and blood-heat reckless movement syndrome in IgAV children, involving seven metabolic

pathways such as lipid and amino acid metabolism. ZHANG et al. [57] conducted serum-urine matched metabolomics on 46 IgAVN(+) patients with persistent proteinuria >0.3 g/d and 44 IgAVN(-) patients with proteinuria <0.3 g/d, identifying choline and cis-vaccenic acid as biomarkers for predicting IgAVN progression.

GENG Yuzuo et al. [58] and BAI Han [59] used urine and serum samples respectively to identify potential biomarkers for differentiating IgAVN and IgAV syndrome types, including tryptophan-methionine, phenylalanine-arginine, phosphatidylcholine, and estrone. These findings demonstrate that metabolomics effectively reflects metabolic states in IgAV, IgAVN, and their TCM syndromes, offering unique advantages for exploring biomarkers and investigating the biological basis of TCM "syndromes." However, most IgAV biomarkers identified through metabolomics remain exploratory clinical findings lacking functional validation and animal experimental confirmation.

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7. Single-Cell Sequencing and Microbiomics Research

Single-cell sequencing accounts for cellular heterogeneity in gene expression by isolating and amplifying individual cells for genomic and transcriptomic analysis to obtain genetic information [64]. One study revealed that immune cell interactions participate in IgAV pathogenesis: acute-phase IgAV children show significant differences in peripheral blood lymphocyte proportions and phenotypes, with upregulated T lymphocyte regulation and activation functions, while mucosal-associated invariant T cell proportions decrease with functional activation [65]. Future research may characterize cell subpopulations through analysis of cellular heterogeneity and unique transcriptomic features to reveal immune cell involvement in IgAV pathogenesis, promote discovery of novel drug targets, and provide basis for new immunotherapeutic strategies.

Microbiomics investigates microbial species, functions, metabolism, and their relationships with disease [66]. Microbiomics studies have found significant differences in microbial species and relative abundance in IgAV patients compared to healthy individuals, suggesting IgAV pathogenesis may involve disease occurrence through microbial alterations. CAO et al. [67] reported that Gram-positive bacteria in the human gut are major drivers of taxonomic shifts associated with IgAV, causing substantial functional impacts. HU Xiaolei [68] found differences in pharyngeal microbiota composition, structure, and functional genes between IgAV and healthy children, suggesting that monitoring dynamic changes in pharyngeal microbial communities may serve as biomarkers for predicting and screening disease risk. Oral and gut microbiota provide new insights for IgAV diagnosis and treatment, though current studies have relatively insufficient sample sizes requiring further validation and disease prediction model construction. Deeper understanding of how microbial community changes interact with the host is needed to continuously explore pathogenic

mechanisms and provide high-level evidence and new therapeutic targets for clinical practice.

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8. Multi-omics Integration

Single-omics studies cannot comprehensively elucidate complex associations among multiple IgAV pathogenic mechanisms, whereas multi-omics integration reveals regulatory relationships across different omics layers through information integration, enabling multidimensional analysis of IgAV. HE Xuelian [69] combined genomics and proteomics to investigate IgAV risk genes and serum proteins predictive of IgAVN, finding MEFV and C1GALT1 genes associated with susceptibility to IgAV and IgAVN respectively, with serum angiotensinogen levels predictive of IgAVN development. XIONG Weilin et al. [70] used microbiomics and metabolomics to analyze bacterial populations and metabolites in saliva samples from IgAV children before and after Yinqiao Powder treatment, finding that Yinqiao Powder may improve oral microecology and treat IgAV by altering Porphyromonas and Veillonella abundance and affecting histidine and phenylalanine metabolism pathways. XIE et al. [71] identified 58 differentially expressed mRNAs and 9 differential proteins between different IgAVN types through RNA sequencing and proteomics, serving as potential biomarkers for IgAVN progression. However, multi-omics integration studies on IgAV remain limited and require further in-depth investigation.

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9. Conclusion and Outlook

The pathogenesis and progression of IgAV are complex and remain incompletely understood. Each omics approach has distinct advantages and limitations. **Advantages:** Identified biomarkers can serve as important references for IgAV diagnosis and prognosis; sequential studies from genomics to transcriptomics, proteomics, and metabolomics enable tracking of IgAV-related information across different biological stages, promoting deeper understanding of pathophysiological processes; omics methods provide strong technical support for exploring the biological basis of different TCM syndrome types; omics investigations of Chinese and Western medicine therapeutic targets facilitate precision medicine implementation. **Limitations:** IgAV omics research remains at the differential molecule screening stage, with some distance from identifying specific biomarkers; all omics studies involve small-sample screening without large-scale, multi-regional validation; current research samples are primarily clinical, lacking experimental animal model validation and in-depth mechanistic studies; standardized bioinformatics methods for large-scale, high-throughput multi-omics data analysis are lacking; additionally, omics technologies require specialized equipment and professional data analysts, increasing research costs.

Currently, IgAV omics research is limited but gradually deepening. Future

trends will focus on: (1) Emphasizing multi-omics integration to comprehensively explore IgAV regulatory networks, identify biomarkers, and achieve precision diagnosis and treatment; (2) Developing single-cell multi-omics to capture multiple omics layers within individual cells, better reflecting complex intracellular interaction networks; (3) Using molecular biology, cellular and immunological approaches to further investigate mechanisms of relevant genes, proteins, metabolites, and pathways; (4) Integrating artificial intelligence, bioinformatics, and data science for multi-omics analysis to systematically capture complex associations among omics data, enabling personalized precision prediction, diagnosis, treatment, and prognosis assessment for IgAV patients. We anticipate that multi-omics technology will achieve major breakthroughs and broader applications in IgAV research.

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