Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Multi-Omics for Rare Kidney Diseases: A systematic review

Christopher Wooster

cwooster01@qub.ac.uk

Queen's University Belfast

Erin Feehily

Queen's University Belfast

Shea Walsh

Queen's University Belfast

Thomas Cahill

Queen's University Belfast

Charuhas Thakar

Queen's University Belfast

Laura Smyth

Queen's University Belfast

Amy Jayne McKnight

Queen's University Belfast

Systematic Review

Keywords: chronic kidney disease, IgA nephropathy, multi-omics, rare condition, rare disease, rare kidney disease, review

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10741167/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Title	**Multi-Omics for Rare Kidney Diseases: A systematic review**
Author's Names (Orchid ID)	Christopher Wooster (0000-0002-0321-9556), Erin Feehily, Shea Walsh (0009-0002-1734-6959), Thomas Cahill (0000-0003-3607-6069), Charuhas Thakar (0009-0004-3970-4600), Laura Smyth (0000-0001-6419-4826), Amy-Jayne McKnight (0000-0002-7482-709X)
Institutional addresses of authors	Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Block A, Royal Victoria Hospital, Belfast, UK, BT12 6BA (Christopher Wooster) Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Block A, Royal Victoria Hospital, Belfast, UK, BT12 6BA (Erin Feehily) Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Block A, Royal Victoria Hospital, Belfast, UK, BT12 6BA (Shea Walsh) Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Block A, Royal Victoria Hospital, Belfast, UK, BT12 6BA (Thomas Cahill) Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, 97 Lisburn Rd, Belfast, UK, BT9 7BL (Charuhas Thakar) Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Block A, Royal Victoria Hospital, Belfast, UK, BT12 6BA (Laura Smyth) Centre for Public Health, Queen's University Belfast, Institute of Clinical Science, Block A, Royal Victoria Hospital, Belfast, UK, BT12 6BA (Amy-Jayne McKnight)
Corresponding Author	Correspondence to: Christopher Wooster cwooster01@qub.ac.uk, Amy Jayne McKnight a.j.mcknight@qub.ac.uk

Multi-Omics for Rare Kidney Diseases: A systematic review

Authors: Christopher Wooster, Erin Feehily, Shea Walsh, Thomas Cahill, Charuhas Thakar, Laura Smyth, Amy Jayne McKnight.

1. Abstract

Rare kidney diseases (RKDs) account for 5-10% of people with chronic kidney disease, collectively affecting millions of people globally. RKDs comprise the majority of childhood kidney disease, disproportionately responsible for ~60% of children who need kidney replacement therapy. RKDs are primarily genetic, so further understanding the molecular mechanisms behind these diseases is crucial to earlier diagnosis, better treatment, and increasing quality of life. Multi-omic approaches provide an opportunity to identify and exploit novel biomarkers and therapeutic targets to aid in the management of RKDs.

The aim of this systematic review is to summarise and evaluate biomolecular multi-omic studies for RKDs internationally from 2014 to 2025.

This systematic review completed searches on PubMed, SCOPUS, Web of Science, BioRxiv and MedRxiv for studies relevant to 'Rare Kidney Disease' and 'Multi-omics' published before the 24th of February 2025. Screening was performed using the Covidence platform, after which data extraction was completed using a customised tool for 19 studies. Of note, neither generic terms 'rare disease' or 'rare kidney disease' were included in the title, abstract, or keyword elements of the articles through to final extraction, highlighting the need to search for each individual kidney disease individually.

Of the 75 RKDs included in the scope of this review, six diseases have a multi-omic study, and 63% of these studies related to one disease, IgA Nephropathy. Whilst ~80% of rare disease have a genetic origin, less than 50% of these studies utilised genetically driven omics technologies. The findings of this review highlight a gap in the research base but also point to opportunities to utilise multi-omic approaches to drive molecular research for RKDs.

Additionally, it reinforces the need for future research on rare diseases to include explicit terms such as 'rare disease' or 'rare condition' in the title, abstract or keywords to maximise their impact and ensure their consideration in future reviews on rare diseases.

Keywords: chronic kidney disease, IgA nephropathy, multi-omics, rare condition, rare disease, rare kidney disease, review

2. INTRODUCTION

Chronic Kidney Disease (CKD), defined as abnormalities of kidney structure or function with implications for health, for at least a three-month period (1), affects more than 7.2 million people in the UK (2) and up to an estimated 850 million people globally, over 10% of the population (3). CKD is often asymptomatic in the early stages with population-based screening sub-optimal. The prevalence is set to grow larger if current trends continue and CKD is predicted to become the fifth leading cause of death by 2040 (4). Prevention and

management of CKD represent a significant financial burden for healthcare systems, especially as medical costs increase sharply as the disease progresses towards kidney failure (5).

In Europe and the UK, the definition of a rare disease is a condition that affects less than 1 in 2,000 people, whilst in the USA this represents a condition that affects fewer than 200,000 patients in the population (6-8). It has been estimated that 80% of these diseases have a genetic origin (9) and whilst each condition is individually rare there are more than 6,000 different conditions, affecting 1 in 17 people in the UK (10). There are at least 150 Rare Kidney Diseases (RKDs) (11, 12). Whilst this only accounts for 5-10% of patients with CKD (12), these RKDs are overrepresented in patients receiving kidney transplant therapy as 25% of these patients are diagnosed with a rare renal condition (12). Additionally, RKDs account for over 60% of kidney failure, and therefore the need for a kidney transplant, in children (13). Increasing our knowledge and understanding of these diseases and how they progress, is key to early diagnosis as slowing the progression towards ESKD which would help improve patient quality of life as well as potentially limiting the financial burden of managing these conditions through novel therapeutic and diagnostic targets.

One opportunity for increasing our understanding of rare diseases, as well as human disease more generally, could be provided by multi-omic analyses, where a disease is studied from multiple different 'omic' perspectives (14, 15). Multi-omic approaches provide an opportunity to investigate rare diseases and interrogate the molecular pathways underpinning these conditions (15). In recent years there has been a shift towards integrating genomic, transcriptomic, proteomic and metabolomic data to improve our understanding of the molecular pathways behind kidney disease as well as to identify potentially novel diagnostic biomarkers and therapeutic targets (16). A 2020 scoping review reported RKDs accounted for only 1.5% of the multi-omic studies on rare diseases published and identified in the previous decade (17).

3. PROTOCOL

This systematic review was designed in accordance with the 2024 Johanna Briggs Institute (JBI) Manual for Evidence synthesis (18) and the completed review followed the PRISMA guidelines (19). As such, the protocol was prospectively registered on PROSPERO (International Prospective Register of Systematic Reviews: registration number: CRD420251063319).

3.1 Eligibility

This systematic review eligibility criteria were developed using the Population, Context and Concept framework set out in the JBI manual; this approach was selected to facilitate broader review of evidence rather than limiting to the more typical Patient, Intervention, Comparison and Outcome framework. The 'population' being considered were patients with a RKD where the primary symptom is CKD (see supplementary material); rare renal cancers were excluded to avoid confusion as these conditions are generally defined by their incidence rate, whereas in the literature, and this review, rare diseases are defined by prevalence. Both males

and females were included, and the individuals were of any age or ethnicity. The 'concept' of this review was biomolecular multi-omic research in RKDs and therefore any study must assess more than one 'Omics'. The 'context' was primary research studies on human participants written in English between 1st January 2014 and 24th February 2025. As our research team are native English speakers, we are not confident including literature published in other languages; we note the JBI guidance for including languages other than English is currently under development (18).

3.2 Search Strategy

Studies were initially identified by searching the following databases. PubMED, SCOPUS, Web of Science and Embase (through Ovid). Pre-Prints were identified using BioRxiv and MedRxiv. The search terms used for PubMed can be found in the supplementary material, these were adapted for the other databases.

Additionally, the 'Rare Kidney Disease' search term in each search was substituted for the search terms associated with each of the 75 RKDs noted in the RKD list in the supplementary material (to develop this list of 75 RKDs we used Orphanet to compile a full RKD list, which was then screened by a multi-disciplinary clinical and research team for RKDs where CKD is a primary rather than secondary symptom). Whilst pre-prints were included, other forms of grey literature were not included in this search strategy as we were primarily interested in capturing peer-reviewed or soon to be peer-reviewed literature. Whilst relevant literature reviews were not included for extraction, reverse citation review of these articles was performed.

3.3 Source of Evidence selection

Studies identified in the initial searches were compiled using the Covidence systematic review management software tool where duplicates were filtered and removed automatically. This was followed by a further manual duplicate screening process to remove those missed by the software. Title, keyword and abstract screening was completed in covidence to remove studies that obviously do not meet the inclusion criteria, as in, they failed to discuss one of the RKDs identified in the inclusion criteria or failed to discuss two or more omics techniques. The articles then underwent full text screening. The full text screening and the Title, keyword and abstract screening processes was completed by two independent reviewers and conflicts were resolved (by a third independent reviewer if necessary) before continuing to the data extraction.

3.4 Data Extraction, analysis and presentation

Data extraction was completed on papers that remained after the full text screening process has been completed using a customised data extraction form (supplementary material 3). Data extracted included Year, first author, manuscript number, Doi, Omics involved, sample source, functional follow-up in in vitro / in vivo animal models, statistical approach for single omics, statistical approach for integrated multi omics (if used), outcome (disease diagnosis, biomarker discovery etc), renal disease involved, cohort involved, sample size, cohort ethnicity and geographical location of cohorts. Bias was evaluated using the revised JBI critical appraisal tool for cohort and case-control studies (20). Upon, completion of data

extraction and analysis the review results were qualitatively and narratively synthesised for presentation below.

4. Results

An overview of the results of our searches and the screening process can be seen in Figure 1 below.

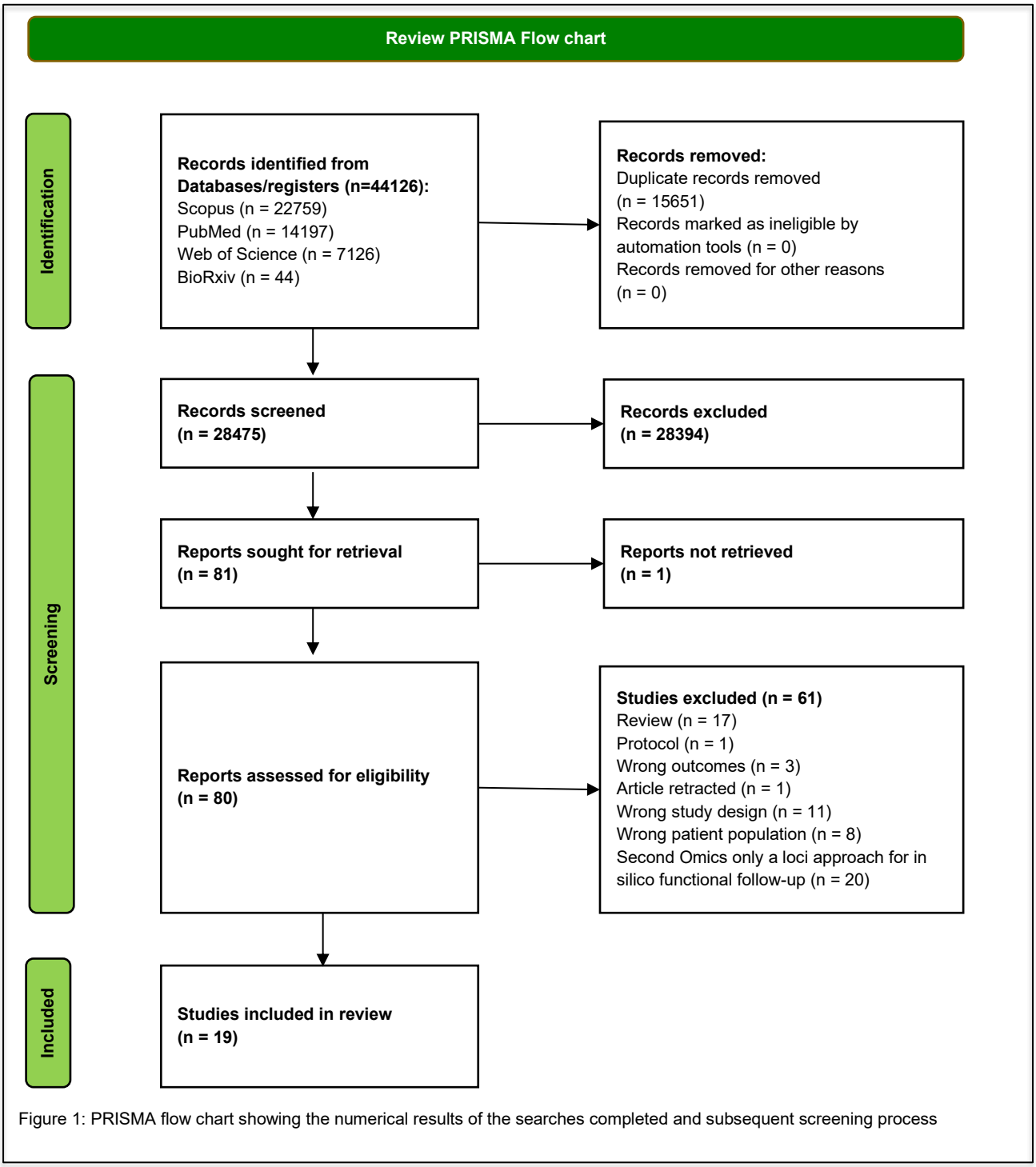


Figure 1: PRISMA flow chart showing the numerical results of the searches completed and subsequent screening process

Searches were conducted in February 2025, and the results were uploaded into Covidence. A total of 44,126 records were recorded upon upload. Of these, 15,651 were identified as duplicates and removed, leaving 28,475 records for title and abstract screening. During title and abstract screening, a further 28,394 studies were excluded, resulting in 81 studies being sought for full-text screening. 80 were retrieved for full text screening, whilst one was unavailable within the timeframe set for retrieval.

Of the 80 retrieved, 11 were excluded for being the wrong study design, eight were excluded as they related to the wrong patient population, three described the wrong outcomes, one article had been retracted since the searches had been complete, and one was a protocol. Additionally, 20 were excluded as the second omic was only used as an approach for in-silico functional follow up and 17 were review articles.

In total 61 studies were excluded leaving 19 studies for data extraction, which was performed using the extraction form (see supplementary material 4 for completed forms). A summary of the studies included for extraction is shown in Table 1.

Interestingly none the studies remaining after full text screening contained the terms ‘rare disease’ or ‘rare kidney disease’ in the title, abstract, keywords or main text, highlighting the importance of our RKD list and the inclusion of explicit search terms for each disease in our search strategy.

Overall, the studies related to six of the 75 RKDs included in our RKD list, 12 were related to IgAN, two were focused on Alport Syndrome and the following four diseases were the focus of one study a piece; Autosomal dominant polycystic kidney disease (ADPKD), Autosomal recessive polycystic kidney disease (ARPKD), ANCA–associated vasculitis and Barrter syndrome (Figure 2). One study investigated CKD more generally but investigated several in-scope RKDs within this context.

Table 1: Summary table of the studies included for extraction after title, abstract and full text screening.

Author (Year)	Disease studied	Study Purpose	Omics used	Key Findings	Comments
Chai (2021) [21]	IgA Nephropathy	Biomarker discovery	Metabolomics & Microbiomics	Significant negative correlations between most clinical parameters and SCFAs levels was observed (All $P < 0.05$). Also, faecal SCFA levels were shown to be significantly lower in patients with IgAN ($P < 0.05$).	Total sample size of 29. Cohort ethnicity not reported.
DeAngelis (2014) [22]	IgA Nephropathy	Biomarker discovery	Metabolomics & Microbiomics	The faecal microbiota and the VOC profiling of Non-progressor IgAN patients were more similar to healthy controls than those of progressor IgAN patients.	Total sample size of 48. Cohort ethnicity reported as Caucasian.
Dong (2022) [23]	IgA Nephropathy	Disease Diagnosis modelling	Metabolomics & Microbiomics	Development and proposal of a diagnostic model for differential diagnosis of IgAN using the microbiome ($P < 0.05$). Additionally potential metabolite biomarkers were identified.	Total sample size of 496. Experimental group sample size is 383. Independent validation group sample size is 58. Blood metabolite group sample size is 55. Cohort ethnicity not reported.
Li (2022) [24]	IgA Nephropathy	Disease Diagnosis modelling	Metabolomics & Microbiomics	Lactobacillus and core metabolites were determined to be predictors of IgAN by an AUC analysis (AUC > 0.79)	Total sample size of 29. Cohort ethnicity reported as Chinese.
Liu (2017) [25]	IgA Nephropathy	Biomarker discovery & underlying mechanism discovery	Transcriptomics & Proteomics	Patient serum creatinine ($P = 0.02$) and eGFR ($P = 0.03$) values significantly correlate with Z scores derived from expression profile of mesangial cell–positive standard genes	Total sample size of 41. Cohort ethnicity and geography not reported.
Neprasova (2016) [26]	IgA Nephropathy	Biomarker discovery	Proteomics & Metabolomics	Showed that a panel of seven markers differentiated patients with IgA nephropathy from patients with other renal diseases and healthy controls.	Total sample size of 38. Cohort ethnicity not available.
Sallustio (2021) [27]	IgA Nephropathy	Biomarker discovery & underlying mechanism discovery	Metabolomics & Microbiomics	Results suggest that the perturbation of mucosal immunity plays a central role in the pathogenesis of IgAN.	Total sample size of 89. Cohort ethnicity reported as Caucasian.
Wang (2021) [28]	IgA Nephropathy	Biomarker discovery	Genomics & Transcriptomics	Identifies GALNT12 as a novel gene associated with Gd-IgA1 ($P=2.383 \times 10^{-9}$). Suggests genetic interactions between GALNT12 and C1GALT1 in IgAN susceptibility.	Total study sample size of 6,232 Cohort ethnicity reported as Chinese. No integrated omics analysis. Gene expression analysis sample size is 86.

Wu (2022) [29]	IgA Nephropathy	Biomarker discovery	Metabolomics & Microbiomics	IgAN patients have significant disturbances of fatty acid and aromatic amino acid metabolism, particularly linoleic acid, arachidonic acid, and tryptophan metabolism	Total sample size of 45. Cohort ethnicity reported as Han Chinese. Aims to build a metabolomic picture of IgAN rather than a truly multi-omic one.
Wu (2021) [30]	IgA Nephropathy	Biomarker discovery	Metabolomics & Microbiomics	Six metabolites were identified which connect the metabolic networks of the gut and blood and are potential targets for further IgAN research	Total study sample size of 45. Cohort ethnicity reported as Han Chinese.
Zhang (2022) [31]	IgA Nephropathy	Biomarker discovery	Proteomics & Metabolomics	New biomarker panel developed and validated using an independent cohort (AUC = 0.91)	Total sample size of 53 for multi-omic analysis. Cohort ethnicity not available.
Wang (2023) [32]	IgA Nephropathy	Biomarker discovery	Metabolomics & Microbiomics	Causality between Actinobacteria class and IgAN was established (P = 0.0029). Relative abundance can differentiate IgAN from other RKDs (AUC = 0.9).	Bioinformatic biomarker discovery sample size is 648,416. Clinical validation study size is 25. Cohort ethnicity not explicitly reported.
Nozu (2014) [33]	Alport Syndrome	Disease Diagnosis	Genomics & Transcriptomics	A combination of genomic and transcriptomic data was used to diagnose Alport syndrome and explain observed phenotype severity.	Total sample size is 11. Cohort ethnicity is reported as Japanese. Diagnostic study only, sample size too small to fully validate diagnostic method.
Wang (2021) [34]	Alport Syndrome	Disease Diagnosis	Genomics & Transcriptomics	Disease Diagnosis	Total sample size is 5. Cohort ethnicity is reported as Chinese. Diagnostic study only, sample size too small to fully validate diagnostic method.
Jones (2017) [35]	ANCA-associated vasculitis	Biomarker Discovery	Epigenomics & Transcriptomics	DNA methylation changes at MPO and PRTN3 further stratify disease remission status (P < 0.001). DNA methylation changes at the PRTN3 promoter are a potential indicator of stable remission (P < 0.001).	Total sample size is 114. Cohort ethnicity is reported as mixed. Results were generated using patient leukocytes, therefore may not be transferable to other cell types
Muto (2022) [36]	ADPKD	Generation of a single cell multi-omic atlas	Epigenomics & Transcriptomics	Identification of potential biomarkers including GPRC5A	Small sample size for purpose (n=13). Cohort ethnicity not reported.
Richards (2024) [37]	ARPKD	Biomarker Discovery	Genomics & Transcriptomics	Increased expression of WNT pathways was associated with disease severity	Total sample size of 28. Cohort ethnicity not available.
Wang (2020) [38]	Bartter Syndrome	Disease Diagnosis	Genomics & Transcriptomics	Disease diagnosis	Sample size is 4. Cohort ethnicity is reported as Chinese. Diagnostic study only, sample size too small to fully validate diagnostic method.

Si (2024) [39]	CKD (includes IgAN, MN and nephrotic syndrome)	Biomarker Discovery	Transcriptomics & Proteomics	Found 32 CKD-related proteins and 20 novel proteins that are associated with CKD, kidney function, and several CKD clinical types.	Cohort ethnicities not explicitly reported. In context of this review results are generalised to CKD and not specific to RKDs

Table 1 Abbreviations List: ADPKD - autosomal dominant polycystic kidney disease; ANCA - antineutrophil cytoplasmic antibodies; ARPKD - Autosomal recessive polycystic kidney disease; AUC - area under the curve; CKD - chronic kidney disease; IgAN - immunoglobulin A nephropathy; MN - membranous nephropathy; RKDs - rare kidney diseases; SCFA - short-chain fatty acids; VOC – Volatile organic compounds

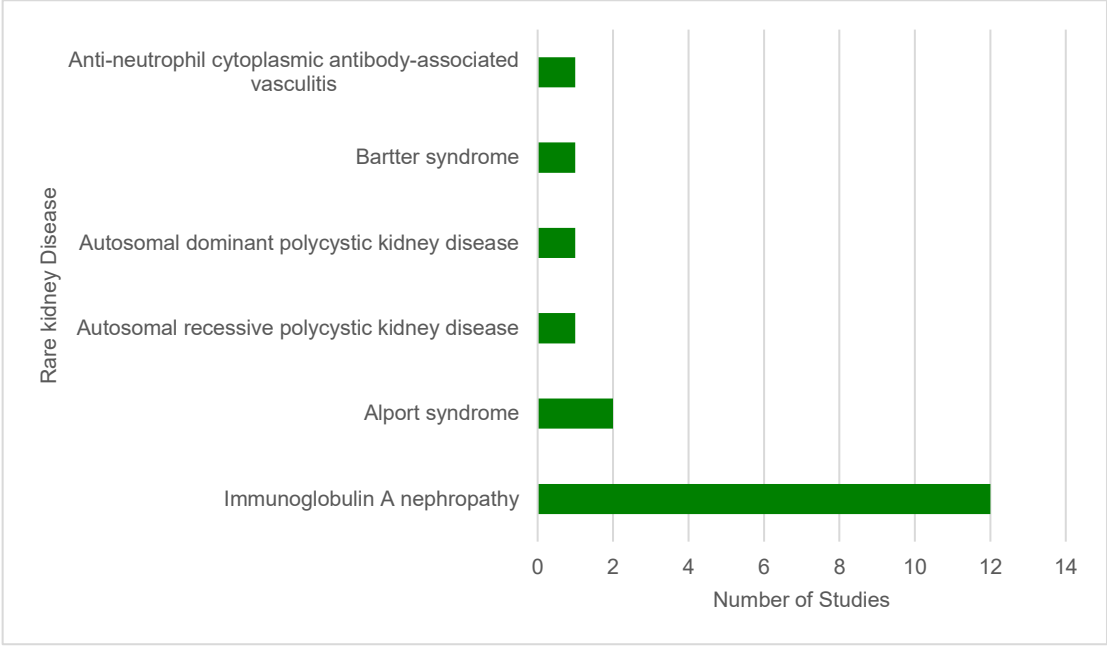


Figure 2: Horizontal Bar chart showing number of studies per disease. NB One study investigated RKDs in the context of CKD and is not included in the above chart

The studies reported a variety of multi–omic analyses including genomics (n=5), epigenomics (n=2), transcriptomics (n=9), proteomics (n=4), metabolomics (n=10) and microbiomics (n=8). Most common combinations of omics were metabolomics with microbiomics (n=8) and genomics with transcriptomics (n=5), whilst various combinations of metabolomics, proteomics, epigenomics and transcriptomics made up the final six. Analyses were performed on a variety of biological samples including biopsies, blood, urine, faeces and in one case, whole kidneys removed during transplant.

The studies originated from Europe (n=4), China (n=9) the USA (n=2) and Japan (n=1) with one study failing to report its geography and two being considered as global studies due to their use of cohorts from across the globe. Despite knowing the locations of all the studies, cohort ethnicity was not reported for 7 studies with the remaining eleven reporting cohorts of mixed (n=2), Caucasian (n=2) Chinese (n=6) and Japanese (n=1) ethnicities.

Outcomes were classified as biomarker discovery (n=14) or disease diagnosis (n=5). Generally sample sizes were small with 12 of the studies reporting total sample sizes of less than 100 (including controls). Three studies recruited more than 100 participants whilst there were two studies (Si et al, 2024, and Wang et al, 2023) that used bioinformatic data from more than 500,000 patients using a combination of existing cohorts from across the globe.

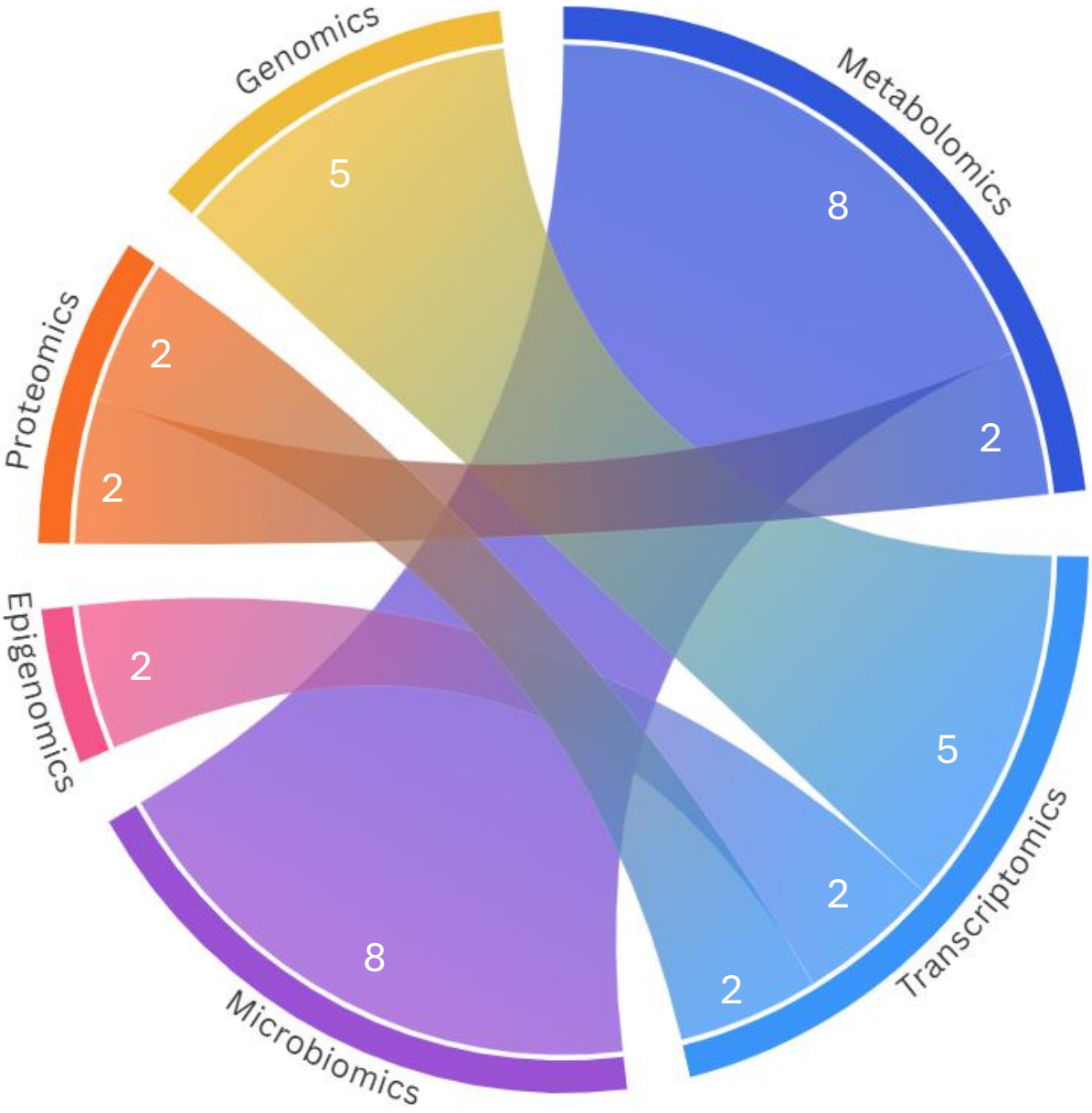


Figure 3: Chord chart showing how different omics were studied in tandem with each other across the literature included in this review

5. Discussion

This systematic literature review has summarised multiomic studies for RKDs, revealing the utility of multiomic approaches to inform diagnosis and to understand more about individual rare diseases. Six of the 75 RKDs that primarily affect the kidneys and lead to kidney failure were the subject of multi-omic studies in the time period investigated and the number of multi-omic studies on these conditions appears to be trending upwards over time with 14 of the 19 studies papers included being published since 2020. As can be observed in Figure 3, a variety of omics combinations were used in the included studies. The most common omic combination was that of Metabolomics and Microbiomics, which may reflect the

overrepresentation of IgAN amongst the studies included. As IgAN is suspected to have a causal microbiomic element in its pathology, exploring the connection between the microbiome and metabolome is an obvious area of interest. However, as 80% of RKDs are suspected of having a genetic origin (40) the fact that less than 50% of the studies utilised genomics was an unexpected result. This again is likely a result of the fact that the multi-omic studies included after screening focus heavily on IgAN but also highlights a key potential direction for exploratory multi-omic research moving forward.

The nine genetically driven (including genomics, epigenomics or transcriptomics) multi-omic studies included in this review highlight a potential pathway in which these types of study can be used to begin to increase diagnostic yields and screen for novel biomarkers and therapeutic targets, especially when a genetic origin is suspected. Conversely, they also highlight the limitation of a lack of diversity in multi-omic layers being investigated per disease. Nozu et al (33) and Wang et al (34) use genomic and transcriptomic methods to diagnose and assess the severity of Alport syndrome, and whilst this is a useful starting point for a known genetic disease, further studies exploring the link between genetic changes and downstream proteomic and metabolic associations may yield further information on potential therapeutic targets and the molecular characteristics of disease progression. The remaining seven studies used combinations of genomic, epigenomic and transcriptomics data to explore genetic biomarkers for their respective diseases with varying degrees of success.

However, several gaps in the existing research base for multi-omic studies in RKDs can be noted, especially in the 75 diseases included on our RKD list. Less than 10% of the diseases included in our list have been researched through multi-omic methods, and with the exceptions of IgAN and Alport syndrome, only one study per disease has been conducted in the 10 years from 2014 to 2025 as such there remains significant scope for further exploratory multi-omic studies on underrepresented RKDs in the future to help identify new ways to diagnose and treat these diseases which account for a substantial minority of CKD cases. Limitations were imposed by small sample sizes as many of these studies were exploratory in nature, as well as this some studies compared omics separately and performed limited integrated analysis. Additionally, cohort ethnicities were not reported in nine of the studies which represents a critical gap in the research literature as people of different genetic backgrounds are known to present different biomarkers for the same illness.

Interestingly, machine learning analysis appears to be used sparingly in the studies included in this review, with ten of the nineteen studies using non-artificial intelligence methodologies for all omic analysis. When it has been used, it is mostly applied to the analysis of individual omics rather than the integrated multi-omic analysis with only Neprosova et al (26) using machine learning methodologies to perform integrated omic analysis in IgAN. This may be because most of the multi-omic studies performed on RKDs in the timeframe assessed were exploratory in nature and analysed small cohorts that are inappropriate for machine learning methodologies. However, it could also represent a lack of familiarity in this type of analysis in the RKD field, especially when combining various different omics data. It should also be noted that the Nepravosa study was designed to conduct integrated multi-omic analysis only.

The risks of bias from the included studies stemmed mostly from small sample sizes, which were on occasion analysed using inappropriate statistical methods. Despite confounders generally being dealt with using detailed exclusion criteria for patient groups, it was noted that several studies did not explicitly address the inclusion and exclusion criteria for control groups leading to a potential bias around how confounders were dealt with. Additionally, due to the cross-sectional, observational nature of the studies included in this literature review each study carries a risk of temporal bias, however, as these were mostly initial exploratory

studies this risk has been deemed acceptable. However, this does highlight an additional gap in the research literature in this field and emphasizes the need for longitudinal registries and biobanks for RKDs on a national and global level. Finally, there are no studies included that report negative results which may be a result of the limited studies included in this review but may also suggest a tendency to report and publish positive results in this field which could lead to issues of publication bias in the case of future biochemical meta-analysis in this area of research.

Despite these limitations the review does highlight the potential power of multi-omic studies in this field of research in the case of IgAN, which was the focus of most of the studies included in this review. IgAN, which despite being classified as rare disease, is the most common form of glomerulonephritis (41) and often progresses to end-stage kidney diseases (ESKD) by the third decade of life. It represents the most common cause of ESKD in young adults (42). The gold standard for diagnosis remains a renal biopsy, however these are rarely performed due to their invasive nature and are not used to regularly assess disease activity.

IgAN can be variable in both its clinical and histopathological presentations but has been described as a systematic disease that develops over four steps: the production of galactose deficient IgA, production of antibodies against galactose deficient IgA, followed by immune complex formation and mesangial deposition on the kidneys (43). Whilst this multi-hit hypothesis was first postulated in 2011, omic studies have further reinforced the assumptions underpinning this understanding of IgAN.

This review highlights the role multi-omic studies can play in providing further evidence to confirm or challenge this hypothesised pathway. Wang et al (28) used genomics and transcriptomic data to identify *GALNT12* as a novel gene associated with Gd-IgA1 and suggested that genetic interactions between *GALNT12* and *CICALT1* impact on Gd-IgA1 levels and susceptibility to IgAN. Whilst in 2017 Liu et al (25) used transcriptomic and proteomic data to show that the expression profiles of mesangial cells correlated with common clinical parameters (eGFR, serum creatine values and segmental glomerulosclerosis).

Neprasova et al (26) and Zhang et al (31) leveraged metabolomic and proteomic data to develop novel protein and metabolite biomarker panels that could potentially be used as an early warning for IgAN and help differentiate it from other renal diseases, although these potential biomarkers require further validation. The remaining eight studies focusing on IgAN used a combination of metabolomics and microbiomics to shed further light on the known association between the microbiome and IgAN status and attempt to elucidate a causal pathway. For example, in 2023 Wang et al (32) used their analysis to suggest that only microbes of the Actinobacteria have a causal relationship with IgAN, and that the relative abundance of these bacteria in IgAN patients can act as a microbial biomarker when attempting to differentiate these patients from those with other glomerular diseases. Additionally, Sallustio et al (27) performed microbiomic and metabolic analysis on urine and faecal samples from Healthy controls, IgAN patients and other non-IgAN glomerulonephritis patients to propose a new hypothesis that microbial dysbiosis leads to a perturbation on mucosal immunity which plays a central role in the pathogenesis of IgAN.

Several of the studies confirmed the known association between microbiome dysbiosis and IgAN, using microbiomics and metabolomics to further map this phenomenon. Li et al (24) for example showed that Lactobacillus and the core metabolites they produce act as predictors of IgAN in area under the curve analysis. Whilst there remains a great need for

validated biomarkers for IgAN, the studies included demonstrate the power of even a limited body of multi-omic research to elucidate and clarify the mechanisms of diseases progression as well as identify potential new biomarkers for the future. However, as noted earlier, this is not the case for the other RKDs on our list highlighting a challenge and opportunity for the field going forward. There remains a gap for different multi-omic studies to help identify biomarkers, therapeutic targets and pathways of disease progression.

This literature review has some limitations that should be noted. Due to the low prevalence of rare diseases individually, many studies use small sample sizes and therefore their findings should be treated with caution until confirmed via the results of further studies. This is compounded by the fact that most of the diseases addressed in this review have only one study and thus only provide one data-point for each RKD studied from a meta-analysis perspective. Lastly, the exclusion of papers not written in English provides the potential for a language bias to be introduced.

6. Conclusion

This systematic review highlights and confirms the previously suspected lack of multi-omic studies on the 75 RKDs included within our list. Less than 10% of the 75 RKDs considered were the subject of a multi-omic study, and over 60% of the studies focused on one disease, IgA nephropathy. This suggests not only a considerable gap in the research base but also a key opportunity to drive forward our understanding of these conditions which represent a sizeable minority of CKD cases and 25% of patients receiving renal replacement therapy.

We have also highlighted a gap in which a genetics-first multi-omic approach can be applied in RKD research. Whilst metabolomics and microbiomics were the most utilised omics combination in the studies included, this was likely a quirk of the high proportion of studies focusing on IgAN. Genetically driven multi-omic studies on Alport syndrome, ARPKD and Bartter syndrome showed this approach to being used to produce higher diagnostic yields and potential biomarkers for these and other diseases of genetic origin. This is especially pertinent considering that approximately 80% of RKDs are thought to have a genetic origin and may represent an initial path forward for future research in this field.

Finally, this review unexpectedly revealed that none of the studies included for extraction contained the terms ‘rare disease’, ‘rare condition’ or ‘rare kidney disease’ explicitly in their title, abstract, keywords or main body. This represents a key opportunity for researchers working on a rare disease to broaden the impact of their work by ensuring future publications on rare diseases explicitly contain these terms which will increase the chances of their work being included in future reviews or policy documents on rare disease more generally. Additionally, it highlights the importance of including explicit search terms for specific conditions in future literature reviews on rare diseases to capture research on specific conditions where the focus is not on rare disease, although it is acknowledged that due to the large number of rare diseases this may not always be possible.

7. List of abbreviations

ADPKD - autosomal dominant polycystic kidney disease

ANCA- antineutrophil cytoplasmic antibodies

ARPKD - autosomal recessive polycystic kidney disease

AUC- area under the curve

CKD - chronic kidney disease

eGFR – estimated glomerular filtration rate

ESKD – end stage kidney disease

IgAN - immunoglobulin A nephropathy

JBI - Joanna Briggs Institute

MN - membranous nephropathy

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

RKDs - rare kidney diseases

SCFA - short-chain fatty acids

VOC – volatile organic compounds

8. Declarations

8.1 Ethics approval and consent to participate

As no primary data was generated, this systematic review does not require ethical approval.

8.2 Consent for publication

Not Applicable

8.3 Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files. Additionally, the search terms can be found in the supplementary material of the protocol for this review which has been uploaded to the Open Science Framework (44)

8.4 Competing interests

All other authors declare no conflicts of interest.

8.5 Funding

This work was funded by a Northern Ireland Department of the Economy Studentship (CW_24; EF_24), The Northern Ireland Kidney Research Fund, the NI Health and Social

Care Research and Development division (COM/5802/24) and LifeArc (10747). These funders had no role in the development or execution of this review.

8.6 Author's Contributions

CW: Conceptualisation (Supporting), Investigation (Lead), Analysis (Lead), Writing – Original Draft (Lead), Writing – Review and Editing (Lead).

EF: Conceptualisation (Supporting), Investigation (Supporting), Writing – Review and Editing (Supporting).

SW: Investigation (Supporting), Analysis (Supporting), Writing – Review and Editing (Supporting).

TC: Analysis (Supporting), Writing – Review and Editing (Supporting).

CT: Conceptualisation (Supporting), Writing – Review and Editing (Supporting).

LS: Conceptualisation (Lead), Writing – Review and Editing (Supporting).

AMcK: Conceptualisation (Lead), Investigation (Supporting), Writing – Review and Editing (Supporting).

8.7 Acknowledgements

Not Applicable

9. References

1. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International. 2024;105(4):S117–S314.

2. Kidney Research UK. Kidney disease: A UK public health emergency - The health economics of kidney disease to 2033. Kidney Research UK; 2023.

3. Mark PB, Stafford LK, Grams ME, Aalruz H, Abd ElHafeez S, Abdelgalil AA, et al. Global, regional, and national burden of chronic kidney disease in adults, 1990-2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. The Lancet. 2025;406(10518):2461–82.

4. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. The Lancet. 2018;392(10159):2052–90.

5. Jha V, Al-Ghamdi SMG, Li G, Wu M-S, Stafylas P, Retat L, et al. Global Economic Burden Associated with Chronic Kidney Disease: A Pragmatic Review of Medical Costs for the Inside CKD Research Programme. Advances in Therapy. 2023;40(10):4405–20.

6. Thomas S, Caplan A. The Orphan Drug Act Revisited. JAMA. 2019;321(9):833.

7. Department of Health and Social Care. The UK Rare Diseases Framework – GOV.UK. London. 2021.

8. European Commission. Rare diseases - Public Health - European Commission [Available from: https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/rare-diseases_en].

9. Olivier Devuyst NVAMK, Giuseppe Remuzzi, and Franz Schaefer for the Board of the Working Group for Inherited Kidney Diseases of the European Renal Association and European Dialysis and Transplant Association. Rare inherited kidney diseases: challenges, opportunities, and perspectives. The Lancet. 2014;383(9931):1844–59.

10. Department of Health and Social Care. England Rare Diseases Action Plan 2022 - GOV.UK. London. 2022.

11. Kerr K, Mcaneney H, Flanagan C, Maxwell AP, Mcknight AJ. Differential methylation as a diagnostic biomarker of rare renal diseases: a systematic review. BMC Nephrology. 2019;20(1).

12. Wong K, Pitcher D, Braddon F, Downward L, Steenkamp R, Annear N, et al. Effects of rare kidney diseases on kidney failure: a longitudinal analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) cohort. The Lancet. 2024;403(10433):1279–89.

13. Kidney Research UK. Collectively common: the devastating impact of rare kidney diseases in the UK. A call for investment, innovation and quality care. 2025.

14. Yamada R, Okada D, Wang J, Basak T, Koyama S. Interpretation of omics data analyses. Journal of Human Genetics. 2021;66(1):93–102.

15. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biology. 2017;18(1).

16. Rroji M, Spasovski G. Omics Studies in CKD: Diagnostic Opportunities and Therapeutic Potential. Proteomics. 2025;25(11-12).

17. Kerr K, Mcaneney H, Smyth LJ, Bailie C, Mckee S, Mcknight AJ. A scoping review and proposed workflow for multi-omic rare disease research. Orphanet Journal of Rare Diseases. 2020;15(1).

18. Aromataris E LC, Porritt K, Pilla B, Jordan Z, editors. JBI Manual for Evidence Synthesis: JBI; 2024 [Available from: https://jbi-global-wiki.refined.site/space/MANUAL.]

19. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349(jan02 1):g7647–g.

20. Barker HT, Hasanoff S, Aromataris E, Stone CJ, Leonardi-Bee J, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for cohort studies. JBI Evidence Synthesis. 2025;23(3):441–53.

21. Chai L, Luo Q, Cai K, Wang K, Xu B. Reduced fecal short-chain fatty acids levels and the relationship with gut microbiota in IgA nephropathy. BMC Nephrology. 2021;22(1).

22. De Angelis M, Montemurno E, Piccolo M, Vannini L, Lauriero G, Maranzano V, et al. Microbiota and Metabolome Associated with Immunoglobulin A Nephropathy (IgAN). PLoS ONE. 2014;9(6):e99006.

23. Dong Y, Chen J, Zhang Y, Wang Z, Shang J, Zhao Z. Development and validation of diagnostic models for immunoglobulin A nephropathy based on gut microbes. Frontiers in Cellular and Infection Microbiology. 2022;12.

24. Li S, Ma C, Yang Y, Cai W, Dai W, Zhang X, et al. Microbiome and metabolome analysis to clarify the interaction between the urine microbiota and serum metabolites in Chinese patients with immunoglobulin A nephropathy. Annals of Translational Medicine. 2022;10(22):1230–.

25. Liu P, Lassén E, Nair V, Berthier CC, Suguro M, Sihlbom C, et al. Transcriptomic and Proteomic Profiling Provides Insight into Mesangial Cell Function in IgA Nephropathy. Journal of the American Society of Nephrology. 2017;28(10):2961–72.

26. Neprasova M, Maixnerova D, Novak J, Reily C, Julian BA, Boron J, et al. Toward Noninvasive Diagnosis of IgA Nephropathy: A Pilot Urinary Metabolomic and Proteomic Study. Disease Markers. 2016; 2016:1–9.

27. Sallustio F, Curci C, Chaoul N, Fontò G, Lauriero G, Picerno A, et al. High levels of gut-homing immunoglobulin A+ B lymphocytes support the pathogenic role of intestinal mucosal hyperresponsiveness in immunoglobulin A nephropathy patients. Nephrology Dialysis Transplantation. 2021;36(3):452–64.

28. Wang Y-N, Zhou X-J, Chen P, Yu G-Z, Zhang X, Hou P, et al. Interaction between G ALNT12 and C1GALT1 Associates with Galactose-Deficient IgA1 and IgA Nephropathy. Journal of the American Society of Nephrology. 2021;32(3):545–52.

29. Wu H, Tang D, Yun M, Liu H, Huang S, Yun C, et al. Metabolic Dysfunctions of Intestinal Fatty Acids and Tryptophan Reveal Immuno-Inflammatory Response Activation in IgA Nephropathy. Frontiers in Medicine. 2022;9.

30. Wu H, Tang D, Zheng F, Li S, Zhang X, Yin L, et al. Identification of a novel interplay between intestinal bacteria and metabolites in Chinese patients with IgA nephropathy via integrated microbiome and metabolome approaches. Annals of Translational Medicine. 2021;9(1):32–.

31. Zhang D, Li Y, Liang M, Liang Y, Tian J, He Q, et al. LC-MS/MS based metabolomics and proteomics reveal candidate biomarkers and molecular mechanism of early IgA nephropathy. Clinical Proteomics. 2022;19(1).

32. Wang F, Li N, Ni S, Min Y, Wei K, Sun H, et al. The Effects of Specific Gut Microbiota and Metabolites on IgA Nephropathy—Based on Mendelian Randomization and Clinical Validation. Nutrients. 2023;15(10):2407.

33. Nozu K, Vorechovsky I, Kaito H, Jun Fu X, Nakanishi K, Hashimura Y, et al. X-linked alport syndrome caused by splicing mutations in COL4A5. Clinical Journal of the American Society of Nephrology. 2014;9(11):1958–64.

34. Wang X, Zhang Y, Ding J, Wang F. mRNA analysis identifies deep intronic variants causing Alport syndrome and overcomes the problem of negative results of exome sequencing. Scientific Reports. 2021;11(1).

35. Jones EB, Yang J, Muthigi A, Hogan LS, Hu Y, Starmer J, et al. Gene-Specific DNA Methylation Changes Predict Remission in Patients with ANCA-Associated Vasculitis. Journal of the American Society of Nephrology. 2017;28(4):1175–87.

36. Muto Y, Dixon EE, Yoshimura Y, Wu H, Omachi K, Ledru N, et al. Defining cellular complexity in human autosomal dominant polycystic kidney disease by multimodal single cell analysis. Nature Communications. 2022;13(1).

37. Richards T, Wilson P, Goggolidou P. Next generation sequencing identifies WNT signalling as a significant pathway in Autosomal Recessive Polycystic Kidney Disease (ARPKD) manifestation and may be linked to disease severity. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2024;1870(7):167309.

38. Wang C, Han Y, Zhou J, Zheng B, Zhou W, Bao H, et al. Splicing Characterization of CLCNKB Variants in Four Patients With Type III Bartter Syndrome. Frontiers in Genetics. 2020;11.

39. Si S, Liu H, Xu L, Zhan S. Identification of novel therapeutic targets for chronic kidney disease and kidney function by integrating multi-omics proteome with transcriptome. Genome Medicine. 2024;16(1).

40. Devuyst O, Knoers MAVN, Remuzzi G, Schaefer F. Rare inherited kidney diseases: challenges, opportunities, and perspectives. The Lancet. 2014;383(9931):1844–59.

41. Mucha K, Pac M, Pączek L. Omics are Getting Us Closer to Understanding IgA Nephropathy. Archivum Immunologiae et Therapiae Experimentalis. 2023;71(1).

42. Penfold RS, Prendecki M, Mcadoo S, Tam FW. Primary IgA nephropathy: current challenges and future prospects. International Journal of Nephrology and Renovascular Disease. 2018; Volume 11:137–48.

43. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The Pathophysiology of IgA Nephropathy. Journal of the American Society of Nephrology. 2011;22(10):1795–803.

44. Wooster C, Feehily E, Thakar C, Smyth L, McKnight A. Multiomics for rare kidney diseases: a systematic review protocol. Open Science Framework. 2026.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials3CompletedExtractionforms.xlsx
- Supplementarymaterials1RareKidneyDiseaseList.xlsx
- Supplementarymaterials2Searchterms.xlsx
- Supplementarymaterials4BiasAnalysisSummaryTable.xlsx