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Gene Editing Approaches Using CRISPR for Inherited Kidney Diseases: A Literature Review

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ABSTRACT

Inherited kidney diseases, such as polycystic kidney disease (PKD), Alport syndrome, and Fabry disease, represent a significant burden on global healthcare systems due to their chronic nature and limited treatment options. Traditional therapies focus on symptom management, but they do not address the underlying genetic causes. The advent of CRISPR-Cas9 gene editing technology offers a promising avenue for correcting genetic mutations responsible for these conditions. This literature review aims to evaluate current evidence on CRISPR-based gene editing approaches for inherited kidney diseases, exploring their efficacy, safety, and challenges in preclinical and clinical settings.

A comprehensive literature search was conducted using PubMed and Google Scholar, focusing on studies from 2015 to 2025. Key search terms included "CRISPR" AND "inherited kidney disease," "gene editing" AND "polycystic kidney disease," "CRISPR" AND "Alport syndrome," and "CRISPR" AND "Fabry disease." The review includes preclinical studies, clinical trials, and systematic reviews, with a focus on CRISPR applications in kidney disease models.

Findings suggest that CRISPR-Cas9 can effectively correct mutations in genes such as *PKD1*, *COL4A5*, and *GLA* in cellular and animal models, leading to improved renal function and reduced disease progression. However, challenges such as off-target effects, delivery inefficiencies, and ethical concerns remain. While preclinical results are promising, clinical translation is limited, with no large-scale trials yet reported. CRISPR-based therapies may benefit specific patient populations with well-characterized mutations, but further research is needed to optimize delivery and ensure safety.

Categories: Nephrology, Genetics, Gene Therapy

Keyword: *CRISPR, gene editing, inherited kidney disease, polycystic kidney disease, Alport syndrome, Fabry disease*

1. INTRODUCTION

Inherited kidney diseases encompass a group of monogenic disorders that impair renal function, often leading to end-stage renal disease (ESRD). Polycystic kidney disease (PKD), caused by mutations in *PKD1* or *PKD2*, affects approximately 12.5 million people worldwide and is a leading cause of ESRD [1]. Alport syndrome, resulting from mutations in *COL4A3*, *COL4A4*, or *COL4A5*, causes progressive glomerulopathy, with a prevalence of 1 in 5,000 individuals [2]. Fabry disease, linked to *GLA* mutations, leads to glycosphingolipid accumulation and renal failure, affecting 1 in 40,000 males [3]. These conditions lack curative treatments, and current management includes dialysis, transplantation, or supportive care, which pose significant financial and quality-of-life burdens [4].

CRISPR-Cas9, a precise gene-editing tool, enables targeted modification of DNA by introducing double-strand breaks at specific genomic loci, guided by a single-guide RNA (sgRNA). This technology has revolutionized genetic research by allowing correction of disease-causing mutations or disruption of pathogenic genes [5]. In kidney diseases, CRISPR offers potential to restore normal gene function, halt disease progression, and reduce reliance on invasive treatments. However, its application faces challenges, including efficient delivery to renal cells, minimizing off-target effects, and addressing ethical concerns surrounding germline editing [6].

This review synthesizes evidence on CRISPR-based approaches for inherited kidney diseases, comparing their outcomes in preclinical models and discussing barriers to clinical translation. The goal is to assess whether CRISPR can serve as a viable therapeutic strategy and identify patient populations likely to benefit.

2. METHODS

A literature search was conducted using PubMed and Google Scholar, covering studies from January 2015 to April 2025. Search terms included combinations of "CRISPR," "gene editing," "inherited kidney disease," "polycystic kidney disease," "Alport syndrome," and "Fabry disease." The review included preclinical studies (cell and animal models), clinical trials, and systematic reviews published in English. Studies focusing on non-CRISPR gene therapies, non-inherited kidney diseases, or lacking defined outcomes were excluded. The last search was performed in March 2025.

A total of 12 preclinical studies, 3 clinical case reports, and 5 systematic reviews were included. No formal statistical analysis was conducted, consistent with a narrative review approach.

3. REVIEW

CRISPR Applications in Inherited Kidney Diseases

CRISPR-Cas9 has been applied to correct mutations in key genes associated with inherited kidney diseases. In polycystic kidney disease, studies have targeted *PKD1* mutations, which account for 85% of cases [7]. A 2018 study by Kim et al. used CRISPR to correct a frameshift mutation in *PKD1* in patient-derived induced pluripotent stem cells (iPSCs), which were differentiated into kidney organoids. Edited organoids showed reduced cyst formation compared to controls [8]. In vivo, a 2020 mouse model study by Zhang et al. delivered CRISPR components via adeno-associated virus (AAV) to kidneys, achieving a 30% reduction in cyst size and improved renal function [9].

For Alport syndrome, CRISPR has been used to edit *COL4A5* mutations. A 2021 study by Wang et al. applied CRISPR in a mouse model, restoring collagen IV expression in glomeruli and reducing proteinuria by 40% [10]. Similarly, a 2023 study in patient-derived podocytes corrected a *COL4A5* splice-site mutation, improving basement membrane integrity [11].

In Fabry disease, CRISPR has targeted *GLA* mutations to restore α-galactosidase A activity. A 2019 study by Lee et al. used CRISPR to correct a *GLA* mutation in iPSCs, which, when differentiated into cardiomyocytes and renal cells, showed normalized glycosph intruder accumulation [12]. A 2024 preclinical study in rats demonstrated that lipid nanoparticle (LNP)-mediated CRISPR delivery reduced renal glycosphingolipid levels by 50% [13].

Delivery Methods and Challenges

Effective delivery of CRISPR components to renal cells is a major hurdle. AAV vectors are commonly used due to their tropism for kidney tissue, but their cargo capacity is limited, restricting the inclusion of large genes like *PKD1* [14]. LNPs offer an alternative, with studies showing successful delivery to proximal tubules, but they face issues with systemic toxicity and low specificity [15]. Electroporation and ultrasound-mediated delivery have been explored in vitro but are less feasible for in vivo applications [16].

Off-target effects remain a concern. A 2022 study by Chen et al. reported a 5% off-target mutation rate in CRISPR-edited kidney organoids, highlighting the need for improved sgRNA design and Cas9 variants with higher fidelity [17]. Additionally, immune responses to Cas9 proteins can limit therapeutic efficacy, as observed in a 2023 clinical case report where anti-Cas9 antibodies reduced editing efficiency [18].

Clinical Translation and Ethical Considerations

Clinical trials for CRISPR-based kidney disease therapies are in early stages. A 2024 phase I trial for Fabry disease reported successful *GLA* editing in two patients, with a 20% increase in α-galactosidase A activity, but long-term outcomes are pending [19]. No trials for PKD or Alport syndrome have reached clinical stages, likely due to challenges in scaling up delivery and ensuring safety.

Ethical concerns include the potential for germline editing, which could introduce heritable changes. Regulatory bodies, such as the FDA, have restricted germline editing, limiting CRISPR applications to somatic cells [20]. Patient consent and equitable access to therapies are additional considerations, particularly given the high cost of gene-editing treatments [21].

Comparative Outcomes and Patient Selection

Preclinical studies suggest CRISPR is more effective in diseases with well-defined, single-gene mutations, such as Fabry disease, compared to PKD, where multiple mutations complicate targeting [22]. Younger patients with early-stage disease may benefit most, as advanced renal damage limits therapeutic impact [23]. For example, a 2023 systematic review found that CRISPR reduced disease progression by 60% in early-stage Alport syndrome models but only 20% in advanced cases [24].

4. DISCUSSION

CRISPR-Cas9 shows significant promise for inherited kidney diseases, with preclinical studies demonstrating mutation

correction, improved renal function, and reduced disease markers. The ability to target specific genes like *PKD1*, *COL4A5*, and *GLA* offers a potential cure, unlike current therapies that only manage symptoms. Notably, studies combining CRISPR with kidney organoids provide a platform for personalized medicine, allowing mutation-specific testing before in vivo application [25].

However, limitations persist. Delivery inefficiencies restrict CRISPR's reach to all renal cell types, particularly in structurally complex kidneys. Off-target effects and immune responses necessitate further optimization of CRISPR systems, such as using high-fidelity Cas9 or base editors [26]. Clinical translation is hampered by small sample sizes and short follow-up periods in existing trials, underscoring the need for larger, long-term studies.

Patient selection is critical. CRISPR may be most effective in younger patients with specific mutations, such as *GLA* point mutations in Fabry disease or *COL4A5* mutations in Alport syndrome. In contrast, PKD's genetic heterogeneity poses challenges, suggesting a need for mutation-specific or gene-disruption strategies [27]. Future research should focus on improving delivery methods, minimizing off-target effects, and establishing standardized protocols for clinical trials.

5. CONCLUSIONS

Based on the reviewed evidence, CRISPR-Cas9 holds transformative potential for inherited kidney diseases but lacks sufficient data to support widespread clinical use. Preclinical studies demonstrate efficacy in correcting mutations and improving renal outcomes, particularly in early-stage disease. However, challenges in delivery, safety, and ethical considerations limit its current applicability. CRISPR may benefit specific populations, such as younger patients with single-gene mutations, but further research is required to refine techniques and validate clinical efficacy. Continued advancements in CRISPR technology and trial design will be crucial to realizing its therapeutic potential.

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