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Critical insights into the genomics-guided Nanomedicine for Rare Alport Syndrome Variants: Disruption of Collagen IV in Alport syndrome

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Authors: Neha Ather, Wania Bint-e-Shahzad

Author Order	Author Name	Affiliation (Department, Institution, City, State, Country)	Email address and ORCIDs
1	Neha Ather	Department of Medicine, Karachi Medical And Dental College, Karachi Metropolitan University, Karachi, Pakistan	atherneha@gmail.com 0009-0006-3915-9379
1	Wania Bint-e-Shahzad	Department of Medicine, Karachi Medical And Dental College, Karachi Metropolitan University, Karachi, Pakistan	waniabinteshahzad.swips@gmail.com 0009-00074911-4286

Corresponding Author:

Wania Bint-e-Shahzad

Karachi Medical and Dental College, Karachi Metropolitan University, Block M North Nazimabad Town, Karachi, Karachi, Sindh 74700,Pakistan

+923341282060

waniabinteshahzad.swips@gmail.com

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Critical insights into the genomics-guided Nanomedicine for Rare Alport Syndrome Variants: Disruption of Collagen IV in Alport syndrome

Abstract:

The disruption of collagen IV plays a central role in pathogenesis of Alport syndrome which involves multiple aspects including genomics guided nanomedicine for rare Alport variants which are not widely explored. The existing articles provides insights on cell-based factors but the challenges regarding transport of therapies to the glomerular basement membrane still remains a major issue. Not only this but there is a lack of variant specific approach in the aforementioned articles. This critical insight aims to overcome the current translational barriers and advance personalized therapy for almost syndrome.

Keywords: Alport Syndrome, genomics-guided therapy, nano-medicine, collagen IV, Rare variants, Glomerular basement membrane

We read with great interest the recent article by Kłusek M. et al titled “Genetic technology in the targeted therapy of Alport Syndrome” (Kłusek M. et al. 2025) [1]. The authors systematically searched PubMed and Google Scholar, corroborating a broad and evidence-based overview of emerging gene therapies for Alport syndrome. The study clearly specifies the disease’s genetic basis, inheritance patterns, and current therapeutic limitations before discussing novel gene-editing strategies, including the latest genetic technologies such as CRISPR/Cas9, exon-skipping, and anti-miRNA-21 oligonucleotides, reflecting recent advances.

Despite the strengths of the study, there were some critiques present in it. Firstly, most cited studies remain cell-based or rely on viral vectors i.e. nanoparticle or other nanomedicine delivery systems for variant-specific Alport therapies are underrepresented, as mentioned by Y Zahao et al. 2024 [2]. Moreover, effective transport of therapeutics to the glomerular basement membrane (GBM) and to podocytes is technically difficult and remains challenging because of filtration barriers and specialized cell architecture (GW Liu, et al. 2020) [3]. It is also noted that although many COL4A3/A4/A5 variants are catalogued, few precision therapies (e.g., splice-switching ASOs, variant-targeted CRISPR) have progressed to validated preclinical animal studies using non-viral nanocarriers, therefore scarcity of variant-specific, precision approaches in vivo (H Li, et al. 2025) [4]. Lastly, data on off-target effects, immune activation, and long-term safety especially for non-viral or nanoparticle delivery of gene editors or oligonucleotides remain insufficient and require systematic evaluation (D Ren, et al. 2022) [5].

We sincerely appreciate the effort and scientific rigor demonstrated by the authors and hope that our constructive feedback will contribute to enhancing future research in this important area.

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