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Article/Review

DECODING THE UMOD GENE: IMPLICATIONS FOR CHRONIC KIDNEY DISEASE THROUGH GENETIC MECHANISMS, DIAGNOSTICS, AND THERAPEUTIC INNOVATIONS

E.N.Tashkenbayeva[1] **M.O.Esankulov**[1]

1. Samarkand State Medical University, Samarkand, Uzbekistan.

Abstract.

This review examines recent advances in the study of UMOD genetic variations, their functional consequences, and their impact on CKD pathogenesis. It also discusses the potential clinical applications of UMOD as a predictive biomarker for early CKD detection, risk stratification, and targeted interventions. The development of transcriptomic, proteomic, and metabolomic approaches allows for a more comprehensive study of UMOD function and its interactions with other genetic and metabolic pathways. Chronic kidney disease (CKD) is a growing global health concern, affecting millions of people worldwide. Genetic factors play a crucial role in the etiology and progression of CKD, influencing susceptibility, disease severity, and treatment response. Among these factors, the UMOD gene, which encodes the glycoprotein uromodulin, is recognized as a key regulator of kidney function, tubular integrity, and disease susceptibility. UMOD polymorphisms affect kidney function by altering sodium transport, modulating immune responses, and regulating oxidative stress, thereby contributing to hypertension, nephron damage, and CKD progression.

Recent GWAS (genome-wide association studies) have confirmed the association between UMOD polymorphisms and an increased risk of CKD and its related complications. Additionally, a significant correlation has been identified between UMOD and hyperuricemia, as uromodulin plays a crucial role in uric acid transport and excretion. **Conclusion**: Personalized medicine based on UMOD genotyping opens new opportunities for individualized risk assessment, tailored pharmacotherapy, and lifestyle modifications to slow CKD progression. Additionally, promising therapeutic strategies are being developed, including pharmacological modulation of UMOD expression and gene therapy. The integration of genetic knowledge with clinical applications highlights the significance of UMOD in CKD pathogenesis and positions it as a promising target for precision nephrology, potentially improving clinical outcomes and optimizing patient management strategies.

Key words: UMOD gene, uromodulin, chronic kidney disease, genetic variations, biomarkers.

Relevence. Chronic kidney disease (ERC) represents a significant global health concern, characterized by a gradual decrease in renal function and a high potential for progression to renal disease in the terminal stage (ESRD). The World Health Organization (2021) has reported that the prevalence of ERC continues to increase, which currently affects approximately 8-16% of the adult population worldwide. This flourishing public health problem is aggravated by associated morbidity, such as cardiovascular diseases and diabetes, further increasing medical care costs and mortality rates [15]. The multifactorial etiology of ERC requires an integral understanding of its underlying mechanisms, including the growing recognition of genetic factors that contribute to the risk of disease and progression.

Among the various genetic components involved in the ERC, the Uromodulin (UMOD) gene has become a critical focus of recent research due to its fundamental role in renal function and its association with hereditary nephropathies. UMOD codifies Uromodulin, a synthesized glycoprotein mainly by renal tubular epithelial cells. This protein performs essential functions in urinary concentration, the modulation of the immune response and the maintenance of tubular homeostasis

[4]. Variations within the UMOD gene have been involved in a spectrum of kidney -related conditions, including hyperuricemic family youth nephropathy, medullary cystic renal disease and, more widely, ERC [14]. Studies have confirmed that the specific polymorphisms of a single nucleotide (SNP) and the variations in the number of copies can influence both the level of expression and the function of the uromodulin, which contributes to the susceptibility of an individual to the ERC to the ERC.

Genetic variations in the UMOD gene may have deep implications for renal pathophysiology observed in ERC. For example, certain variants can alter the stability of the protein and its interaction with intratubular factors, which can lead to a renal interstitial lesion and tubulointersticial fibrosis, a distinctive seal of the ERC progression [6]. In addition, it is known that the product of the UMOD gene has roles in the regulation of sodium reabsorption in the nephron ERC [13]. These mechanistic ideas underline the importance of the variations of the UMOD gene not only in the development of the ERC but also in the understanding of the individual responses of the patients to the therapeutic interventions.

In addition, the genetic foundations of the ERC extend beyond the mere susceptibility; They also cover considerations for diagnostic strategies and treatment paradigms. Advances in genetic tests and association studies of the entire genome (GWAS) have facilitated the identification of UMOD variants as potential biomarkers for the diagnosis and prognosis of ERC. These genetic ideas could lead to more personalized approaches in the management of ERC, guiding clinical decision making in the prevention and treatment of kidney disease [8]. The current research focuses on taking advantage of these genetic markers for detection purposes, which can allow previous detection and intervention in populations at risk.

In light of these developments, future research addresses will probably cover several key areas. The exploration of genetic-environment interactions, the functional characterization of the newly identified UMOD variants, and the potential for translation of gene editing technologies present exciting opportunities to intervene in ERC at the genetic and phenotypic level. In addition, the therapeutic strategies destined to modulate uromodulin levels, either through small molecules or biological products, represent a promising way for the development of ERC innovative treatments, addressing the genetic and symptomatic aspects of this complex disease., The Umod gene, located on chromosome 16, encodes u umodulin, a glycoprotein secreted mainly by the renal tubular cells of the thick lop of the Henle loop. Uromodulin is the most abundant protein in urine and plays a critical role in renal function and homeostasis. Its functions include modular inflammatory response, sodium handling regulation, influence urinary concentration and contribute to the maintenance of the epithelial barrier within the renal tubules [17]. In addition, uromodulin is implied in the prevention of urinary tract infections and formation of kidney stone, indicating its multifaceted importance in kidney health.

Changes in the Umod gene may have deep implications for renal function and the development of chronic kidney disease (CKD). Variants in this gene have been associated with increasing susceptibility to various renal pathologies, usually through mechanisms that disturb normal cell processes. For example, specific mutations in UMOD may lead to the unfolding and aggregation of ureodulin, which has been shown to start the stress of the endoplasmic reticulum (ER) and activate the unfolded protein response. This waterfall of cellular events can culminate in tubular lesions and fibrosis, finally contributing to the loss of nephrons and the progression of the CKD [12,17].

The research has shown that common variants such as single nucleotide polymorphism RS12917707 (SNP) are associated with high urinary urinary levels and an increased risk of developing CKD [7]. The mechanism underlying this correlation seems to involve the regulation of sodium transportation in the renal tubules, where altered levels of Umomodulin can affect the activity of the main sodium carriers, such as the NA-K2Cl Cotransporter. The deregulation of these carriers can lead to untied changes in tubular function and an imbalance in electrolytic homeostasis, both critical factors in the DRC pathogenesis.

In addition, interactions between ureodulin and renal inflammation are receiving increasing attention as a potential way through which UMOD variants can influence kidney disease. High uromoduline urinary levels correlated with inflammation markers were found, suggesting that

ureodulin could play an attenuating role in inflammatory responses or, conversely, to exacerbate them in pathological conditions [17]. Understanding the bidirectional relationship between ureodulin and inflammation remains in the forefront of current research enterprises, particularly in relation to their implications for the development and progression of the CKD.

From a diagnostic perspective, the evaluation of urine levels in urine emerged as a biomarker potential for the progression of the CKD and a means of elucidating the underlying pathological processes associated with Umod variations. Studies are increasingly focused on the predictive value of urinary urinary concentrations as a noninvasive method to monitor kidney health and disease progression [1,5]. Identification of patients with mutations in UMOD can allow personalized monitoring strategies and targeted interventions, paving the way for more effective CKD management.

As the field continues to evolve, future research is ready to unravel the complex interaction of genetic variations in UMOD and its general implications for the CKD. Investigations on new therapeutic approaches that modulate the activity of ureodulin or improve their protective functions while mitigating their pathogenic effects are of paramount importance. Such enterprises can lead to innovative treatment strategies adapted to patients with specific a variant, performing promises for better results in those afflicted with chronic kidney disease [11]., Current research increasingly focused on specific genetic variants within the Umod gene and its influence on chronic kidney disease (CKD). The Umod gene, located on chromosome 16, encodes u umodulin, a glycoprotein that is abundantly expressed in the thick ascending member of Henle's loop in the kidneys. The variants of this gene were implicated in the etiology of various forms of CKD, mainly by mechanisms that affect renal function and morphology.

One of the most extensively studied mutations in the Umod gene is RS4293393, a single nucleotide polymorphism (SNP) that showed a significant association with CKD susceptibility. Mira et al. (2025) elucidated that the prevalence of this variant may vary between populations, with a higher frequency observed in certain ethnic groups. It has been shown that this variant influences urine levels in the urine, which in turn may reflect renal tubular function. The altered expression of Umomodulin due to the presence of RS4293393 may interrupt normal regulatory mechanisms within nephron, leading to untamed responses that promote renal fibrosis and decline in glomerular filtration rate (TGF).

Genetic Variations of UMOD and Their Implications in CKD

Mutations in UMOD can lead to protein misfolding, triggering endoplasmic reticulum stress and activating the unfolded protein response (UPR), resulting in tubular damage and interstitial fibrosis. These mechanisms underline the importance of UMOD in CKD pathogenesis and highlight its potential as a therapeutic target. Furthermore, recent studies suggest that UMOD variants contribute to electrolyte imbalance, inflammation, and renal fibrosis, which exacerbate disease progression [3].

UMOD in CKD Diagnostics and Biomarkers

Proteomic and metabolomic analyses further enhance our understanding of UMOD's role in CKD by identifying specific protein signatures associated with genetic variants. These findings support the integration of UMOD biomarker assessment into routine clinical practice for risk stratification and early intervention. Additionally, recent studies highlight the potential of urinary and serum uromodulin as predictive biomarkers for CKD-related cardiovascular complications, further emphasizing its diagnostic significance [18].

Therapeutic Implications and Future Directions

Recent research also highlights the potential of small molecule therapies that stabilize or enhance uromodulin function, reducing fibrosis and inflammation [17]. Studies are investigating the role of sodium transport inhibitors in mitigating UMOD-induced sodium retention, offering a promising avenue for therapeutic intervention. Moreover, combination therapies targeting UMOD along with renin-angiotensin-aldosterone system (RAAS) inhibitors could provide synergistic benefits in slowing CKD progression [14].

Future research should focus on elucidating gene-environment interactions that influence UMOD function, optimizing genetic screening for personalized medicine, and validating UMOD-based therapies in clinical trials. Expanding biorepositories and conducting longitudinal studies will

further refine our understanding of UMOD's impact on CKD progression. The application of artificial intelligence in analyzing large-scale genetic and proteomic data could also enhance predictive models for CKD risk assessment and treatment personalization [20].

Conclusion. In terms of diagnostic strategies, the identification of specific variants can facilitate the development of genetic screening approaches to stratify the risk between individuals predisposed to the CKD. The use of next -generation sequencing technologies has allowed researchers to evaluate the frequency of these variants in various populations, allowing the identification of at risk populations and early intervention potential [3]. In addition, serum and urinary biomarkers related to Uromoduline expression levels are being explored as potential diagnostic tools that can complement existing clinical parameters, increasing accuracy in DRC diagnosis and treatment.

Current research emphasizes the need for comprehensive studies designed to delineate the functional consequences of various mutations of UMOD and its interactions with environmental factors, which could collectively illuminate the complete scope of genetic contributions to the CKD [16,18]. Investigations focused on gene-environment interactions will be fundamental, as they can reveal how lifestyle factors or comporbid conditions exacerbate or mitigate the effects of UMOD's deletine variants.

In the therapeutic front, there are increasing interests in modulation of uromodulin roads as a new treatment strategy for the CKD. Pharmacological agents directed to the expression or function of ureodulin can potentially alleviate the progression of the CKD, restoring homeostasis in renal physiology. Encouraging preclinical models have shown that increased levels of uruomodulin can reduce tubular lesion and fibrosis, presenting a promising therapeutic avenue for future exploration [1]. In addition, genetic therapy approaches aimed at correcting or compensating pathogenic variants of UMOD can offer transformational impacts on CKD management.

Investigation on the way in the genetic foundations of the CKD through the lenses of the variants UMAD not only increases the understanding of the pathology of kidney disease, but also maintains significant implications for precision medicine. By advancing knowledge around genetic contributions and developing targeted diagnosis and treatment strategies, future research ventures can benefit exclusively doctors and patients, leading to better results in chronic kidney disease management [2].

The UMOD gene plays a pivotal role in CKD susceptibility, progression, and potential therapeutic intervention. Genetic insights into UMOD variations enhance diagnostic accuracy and open avenues for precision medicine in CKD management. Continued research is essential to translate these findings into effective clinical applications, ultimately improving outcomes for CKD patients worldwide. Understanding the complex interactions between genetic predisposition and environmental factors will be crucial in developing more effective and individualized CKD treatment strategies.

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