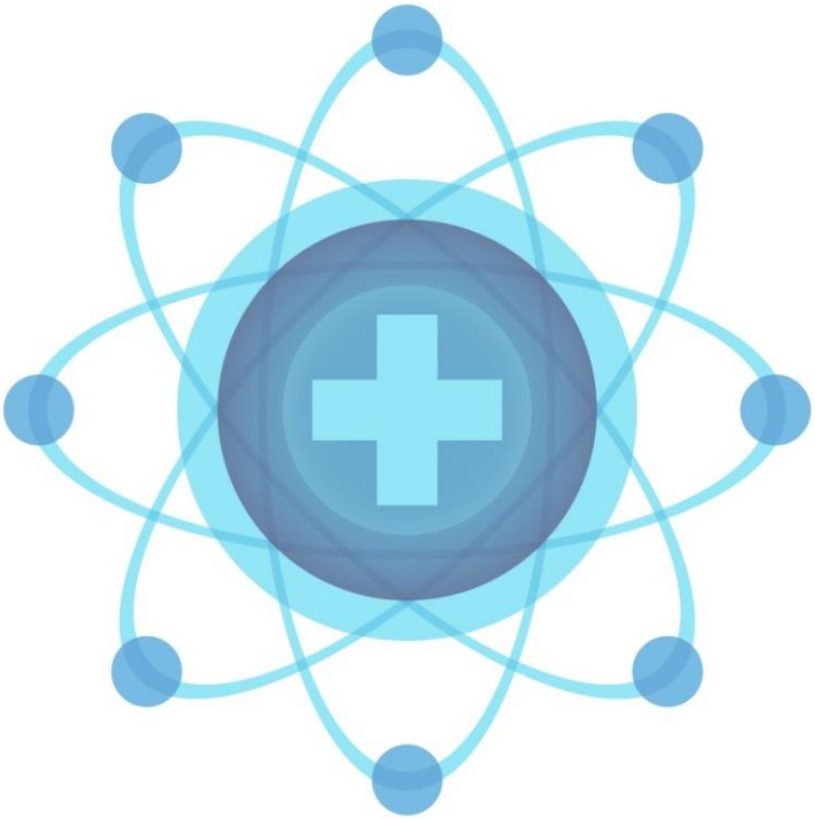

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MODERN VIEW ON THE PROBLEMS OF GENETIC PREDISPOSITION TO NEPHROPATHY WITH VARIOUS ETIOLOGIES. (Literature review)

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Abstract. Today, the problems of genetic predisposition in the etiology of all non-communicable diseases are widely discussed. Also, numerous scientific studies have shown that kidney genetic changes play an essential role in the occurrence and development of chronic diseases. This article analyzes several scientific publications on the clinical and diagnostic significance of molecular genetic changes in various etiologies' development of chronic kidney diseases.

Keywords: chronic kidney disease, diabetic nephropathy, chronic glomerulonephritis, hypertension, microRNA, APOL L1, endothelial dysfunction.

Chronic kidney disease (CKD) is a progressive decline in kidney function that is either directly related to primary kidney disease or secondary to hypertension, diabetes, and obesity. According to epidemiological reports from the US Centers for Disease Control and Prevention, the prevalence of CKD is 15% in the US adult population and is expected to continue to rise in the future, whichincreases the burden on the healthcare system (SDS, 2019)

End-stage renal disease (ESRD) occurs when the estimated glomerular filtration rate (GFR) falls by at least 10% of normal. Among the main factors in the progression of kidney damage in obesity are: insulin resistance (IR), hyperinsulinemia, dyslipidemia, impaired systemic and renal hemodynamics, ischemia of kidney tissues, auto- and paracrine effects of adipose tissue hormones [1, 28–29].

Obesity-associated kidney disease with diabetes develops when several metabolic and hemodynamic factors interact, activating common intracellular signals, which, in turn, cause the production of cytokines and growth factors that form kidney failure. The mechanisms underlying glomerular hyperfiltration in the presence of obesity are widely discussed in the literature [1]. The recognized mechanism is data on an increase in sodium reabsorption in the immediate vicinity of the tubules or the loop of Henle, leading to the development of tubuloglomerular feedback - an indirect decrease in the resistance of afferent arterioles, an increase in intracapsular pressure and glomerular filtration rate [27].

There are studies that show a decrease in glomerular hyperfiltration and damage to kidney tissue with weight loss [31]. The determination of markers of endothelial dysfunction is currently relevant in many diseases, including kidney diseases [32].

Diabetes mellitus (DM) is a common chronic complex disease of rapidly growing global importance, with many complications including retinopathy, neuropathy and nephropathy. Until 2017, the International Diabetes Federation (IDF)

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reported that around 452 million adults worldwide suffer from diabetes, and by 2045 this number could increase to 629 million[3,5]. Diabetic nephropathy (DN) is one of the most common microvascular complications of DM and a leading cause of ESRD, leading to high morbidity and mortality. The main pathological changes in DN are the accumulation of advanced glycation end products (AGEs), growth factors, and hemodynamic and hormonal variations that lead to proteinuria, hypertension, and a permanent decline in kidney function. However, previous research has shown that approximately 30-40% of patients with DM progress to ESRD [3,4], suggesting that genetic variations may influence the initiation and development of DN and ESRD. It is well known that gene susceptibility to DN plays an important role in humans, even under the same environmental exposure. Family clustering also confirms the importance of hereditary factors in DN and ESRD. Therefore, many genetic studies have been carried out to identify potential candidate genes in large diabetic cohorts [6], which may facilitate the study of the pathogenesis of DN. With the development of genetic methods, including studies of linkage and candidate genes, as well as studies of the study population, type of diabetes and phenotypes, it is not easy to understand the real effect of genetic variants. suggesting that genetic variation may influence the initiation and development of DN and ESRD. It is well known that gene susceptibility to DN plays an important role in humans, even under the same environmental exposure. Family clustering also confirms the importance of hereditary factors in DN and ESRD. Therefore, many genetic studies have been carried out to identify potential candidate genes in large diabetic cohorts [6], which may facilitate the study of the pathogenesis of DN. With the development of genetic methods, including studies of linkage and candidate genes, as well as studies of the study population, type of diabetes and phenotypes, it is not easy to understand the real effect of genetic variants. suggesting that genetic variation may influence the initiation and development of DN and ESRD. It is well known that gene susceptibility to DN plays an important role in humans, even under the same environmental exposure. Family clustering also confirms the importance of hereditary factors in DN and ESRD. Therefore, many genetic studies have been carried out to identify potential candidate genes in large diabetic cohorts [6], which may facilitate the study of the pathogenesis of DN. With the development of genetic methods, including studies of linkage and candidate genes, as well as studies of the study population, type of diabetes and phenotypes, it is not easy to understand the real effect of genetic variants. even under the same environmental conditions. Family clustering also confirms the importance of hereditary factors in DN and ESRD. Therefore, many genetic studies have been carried out to identify potential candidate genes in large diabetic cohorts [6], which may facilitate the study of the pathogenesis of DN. With the development of genetic methods, including studies of linkage and candidate genes, as well as studies of the study population, type of diabetes and phenotypes, it is not easy to understand the real effect of genetic variants. even under the same environmental conditions. Family clustering also confirms the importance of hereditary factors in DN and ESRD. Therefore, many genetic studies have been carried out to identify potential candidate genes in large diabetic cohorts [6], which

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Hypertension is the second leading cause of ESRD after diabetes mellitus. According to statistics published by the US Renal Data System, hypertension accounts for 26% of post-diabetic ESRD patients, accounting for 38% [7,9,15]. Interestingly, the incidence of ESRD differs according to ethnic origin. Hypertension has been reported as a cause of ESRD in 35% of African Americans compared to only 25% of Caucasians in the US [2,11,18]. More recent studies have shown that African Americans are three times more likely to develop kidney disease than whites, especially those associated with hypertension, as they often develop CKD when systemic blood pressure rises to the range of mild to moderate hypertension at a young age [5,13, 27]. Another conclusion is that that hypertensive kidney disease is significantly more common among first- and second-degree relatives of patients with CKD than in individuals without a family history of CKD, suggesting that the predisposition of renal failure to hypertension is segregated in families [15,21,31]. These data indicate that progression to ESRD in hypertension is, at least in part, determined by hereditary factors. Kidney function can often be altered by altering renal hemodynamics, producing renal reactive oxygen species (ROS), promoting kidney fibrosis and inflammation, and decreasing podocyte function in hypertension, diabetes, obesity, and aging [4,17,19]. Regardless of underlying mechanisms , these studies provide an opportunity to manage the progression of CKD in patients with hypertension by changing the expression of causative genes, determining hereditary susceptibility. This review summarizes recent findings that highlight the identification of some of the genetic factors underlying susceptibility to hypertensive kidney disease in animal and human studies [9,16,25,32].

Endothelial dysfunction in CKD patients is considered as an imbalance between vasoconstrictors and relaxing factors, between anti- and procoagulant mediators, growth factors and their inhibitors [33]. The relationship of endothelial dysfunction (ED) with kidney damage seems to be natural, but insufficiently studied. The pathological role of endothelial dysfunction has been described in chronic pyelonephritis and chronic glomerulonephritis [34].

Currently, endothelial dysfunction is understood as an imbalance between the production of vasodilating, athrombogenic, antiproliferative factors, on the one hand, and vasoconstrictor, prothrombotic, and proliferative substances produced by the endothelium, on the other [34]. Decreased endothelial synthesis of nitric oxide (NO), increased levels of endothelin-1, circulating von Willebrand factor, plasminogen activator inhibitor, homocysteine, thrombomodulin, soluble molecule of vascular intercellular adhesion B1, C-reactive protein, microalbuminuria, and others are considered markers of endothelial dysfunction [35] .

It has been proven that kidney disease progresses in patients with hypertension with the formation of nephrosclerosis and the development of a primary wrinkled

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kidney. In DM 2, tubulointerstitial fibrosis, glomerulosclerosis, and diabetic nephropathy develop [12–14].

In the era of modern medicine, fundamental scientific principles have been formed in the diagnosis of kidney diseases, which are based mainly on morphological research methods: light microscopy, immunofluorescence and electron microscopy. However, in recent decades, these methods have become insufficient for the verification of various diseases, especially those with an atypical clinical picture. Currently, molecular diagnostic methods have begun to actively develop, which not only complement traditional research methods, but also provide insight from the point of view of molecular pathophysiology.

It is expected that improving sequencing technologies, as well as the development of transcriptomics, provided by the introduction of new opportunities (Nanostring) for studying gene expression not only in fresh, but also in fixed and paraffin-embedded tissues, will play an increasingly important role in the diagnosis of kidney diseases [1] The nCounter technology from Nanostring technologies is based on the classical method of molecular biology - photofixation of fluorescent labels on specific molecules. In this case, the labels have a special structure, namely, an exciting target molecule and a reporter (i.e., directly fluorescent) part. Due to this, with a known structure of the product, there are practically no restrictions on the design of the research panel: it can include both DNA and RNA or proteins. This opens up the broadest horizons for obtaining large amounts of data with a small amount of incoming product. With constantly improving methods of manual and machine data processing, the indicators obtained using nCounter will be relevant for a long time. This technology is aimed at obtaining an absolute result - data on the content of the target in a particular tissue or cell. Such data can be repeatedly reused even with a significant expansion of the sample, since they have normalization flexibility, which is essential for the assimilation of research results by the scientific community. will be relevant for a long time. This technology is aimed at obtaining an absolute result - data on the content of the target in a particular tissue or cell. Such data can be repeatedly reused even with a significant expansion of the sample, since they have normalization flexibility, which is essential for the assimilation of research results by the scientific community. will be relevant for a long time. This technology is aimed at obtaining an absolute result - data on the content of the target in a particular tissue or cell. Such data can be repeatedly reused even with a significant expansion of the sample, since they have normalization flexibility, which is essential for the assimilation of research results by the scientific community.

The greatest interest in the field of molecular medicine today is the study of dynamic products, which primarily include RNA. Nanostring provides an opportunity to study any of its types, including non-coding miRNAs. To date, there are methodological options for studying the distribution of RNA products in various tissues, including archival, formalin-fixed waxed samples, and even in a single cell (single cell). At the same time, in terms of the accuracy of the data obtained, this technology is comparable to real-time polymerase chain reaction (PCR), and in terms of performance, it is comparable to Next-Generation Sequencing (NGS).

Such a solution to a complex technical problem makes it possible to identify many diagnostic problems, and the widespread introduction of transcriptomics methods will require continuous collaboration between clinicians, molecular biologists, geneticists, and morphologists. Many kidney diseases currently have a morphological, immunological and clinical classification, which often does not explain the underlying pathophysiological mechanisms. Despite its strengths, morphological evaluation is limited in the interpretation of kidney lesions with non-specific etiological associations [2]. These limitations jeopardize the ability to establish an accurate diagnosis and prescribe effective treatment [2, 3].

The development of molecular diagnostic methods increasingly opens up prospects for a personalized approach to the study of pathology at various levels of interaction; these achievements provide a qualitative assessment of DNA, RNA, proteins, and their metabolites, which makes it possible to determine new biomarkers [1]. Thus, the need for molecular diagnostics is gradually moving into the daily clinical practice of examining nephrological patients.

A convincing example is the improvement in the diagnosis, prognosis, and principles of therapy for membranoproliferative glomerulonephritis [1]. Traditionally, this disease is divided into three types: I, II and III, depending on the location and characteristics of ultrastructural changes in the glomerular basement membranes. Currently, it is known that in types I and II, the deposition of the C3 component of the complement takes place, which is etiologically mediated by its activation along an alternative pathway [4]. Type I is characterized by an unchanged lamina densa in the glomerular basement membrane and the predominant presence of subendothelial deposits of the C3 component - C3 glomerulonephritis, which, together with type II (dense deposit disease), is included in the wider group of C3 glomerulopathies [5]. One of the key roles in the pathogenesis of the development of the disease is played by factor H, which is the main regulator of the alternative complement pathway. In addition, this factor has been shown to prevent complement activation on the cell surface, while mutations in the N-terminal region of factor H lead to uncontrolled complement activation on endothelial cells, which ultimately leads to the development of C3 glomerulopathies [5]. Identification of specific genetic mutations in patients allows the use of personalized methods of treatment: monoclonal antibodies, “complement factor H-therapy”, etc. [4, 5].

The study of the causes of the development of nephrotic syndrome is primarily associated with studies that determine the state of the proteins of the slit membrane of podocytes, namely, the identification of mutations in the genes encoding these proteins. It has been experimentally and clinically proven that the mutation of the genes that regulate the state of these proteins underlies the hereditary forms of nephrotic syndrome [7].

One of the important proteins of the podocyte cytoplasm is α-actinin-4. This protein is found both in the kidneys and in the walls of blood vessels and functions to bind the protein complex of the slit membrane of the podocyte and the protein complex of the glomerular basement membrane. The role of α-actinin-4 in the pathogenesis of proteinuria has been noted [2].

In the last decade, the role of miRNAs in the pathogenesis of kidney diseases has attracted great interest from researchers. MicroRNA is represented by short noncoding RNA molecules with a length of approximately 22 nucleotides, which regulate gene expression at the posttranscriptional level by RNA interference [11]. Several types of microRNAs have now been found in humans, as well as in plants, animals, and some viruses. The main role of microRNAs is to regulate a wide range of cellular functions, including cell proliferation and apoptosis. In addition, data on the role of miRNAs in the pathogenesis of many human diseases began to accumulate in the world literature [12, 23]. Microarray analysis of rat and human tissues showed that a number of miRNAs, such as miR 192, miR 194, miR 204, miR 215 and miR 216, are found mainly in the renal tissue and play an important role in maintaining kidney homeostasis under physiological and pathological conditions [24]. Over the past 10-15 years, several basic and clinical studies have been carried out, indicating that the level of specific miRNAs in the renal tissue and peripheral blood lymphocytes changed in various kidney diseases [14,29].

Both in vitro and in vivo, the critical role of miRNAs, including miR-25, miR-29, miR-192, miR-377, and miR-45, in the pathogenesis of diabetic nephropathy has been shown. In addition, pathological expression of miR-148b was found in peripheral blood mononuclear cells, probably due to high glycosylation of IgA1 into IgA and on the other hand miR-29c expression upon activation of transforming growth factor beta-1 (TGF-beta1), which plays one of the key roles in formation of interstitial fibrosis of the kidneys [16,32].

A variety of microRNAs play an important role in the initiation and progression of kidney disease. At the same time, the level of expression of specific microRNAs in peripheral blood can be regarded as molecular biomarkers of the development of nephrological pathology [17,23,31]. C. Zhang et al. (2015) studied miRNA expression in blood serum in focal segmental glomerulosclerosis and found that miR-186 expression level correlates with the level of proteinuria and can be used as a biomarker in this disease [18,21,35].

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD), with the risk of CVD mortality gradually increasing as kidney function declines. Compared with European Americans, African Americans are at increased risk for all-cause mortality and cardiovascular disease associated with CKD. Although there are racial differences in traditional risk factors and quality of care, genetic predisposition may also contribute.

Among African Americans, risk variants in the gene encoding apolipoprotein L1 (APOL L1) have been associated with many types of kidney disease. Parsa and colleagues reported in the African American Study of Kidney Disease and Hypertension (AASK) that individuals with 2 copies of APOL L1 (G1 and G2) high-risk variants had an almost 2-fold greater risk of CKD progression compared with individuals with and without 1 copy him. It is unclear whether these risk variants are associated with an increased risk of cardiovascular disease, as the results of the few studies available are conflicting. In the Jackson Heart Study (JHS), the Women's Health Initiative (WHI), and the Cardiovascular Heart Study (CHS), high-risk APOL

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L1 variants were associated with an increased risk of adverse cardiovascular disease. It is important to note that the way remains unknown,

Accelerated and malignant forms of hypertension, atheroembolic kidney disease, and renovascular hypertension are well-documented causes of CKD that develop in people with hypertension. With these diseases, kidney function can quickly decline. However, the notion that mild-to-moderate essential hypertension is a common initiator of CKD is at best unconvincing. The discovery of an association between the apolipoprotein L1 gene (APOL L1) and non-diabetic nephropathy in populations of recent African ancestry confirms that CKD usually develops first, followed by an increase in systemic blood pressure [8,13,22].

Renal risk APOL L1 genotypes are known to be associated with a spectrum of diseases associated with focal segmental glomerulosclerosis (FSGS); these include indurated glomerulosclerosis with minimal or no proteinuria (a disease often misattributed to hypertension), collapsing glomerulopathy, severe lupus nephritis, sickle cell nephropathy, and more rapid renal allograft failure depending on the genotype of the kidney donor. Clearly, many African American participants in AASK who had advanced CKD had primary kidney disease rather than hypertension-associated nephropathy. Many cases with minimal or no proteinuria appeared to be caused by APOL L1., including indurated glomerulosclerosis and FSGS, as reported in the AASA kidney biopsy study [15,20,28].

African Americans have a significantly higher risk of hypertensive and diabetic nephropathy. Numerous studies have focused on identifying genetic variants that are expressed differently in African Americans. APOL L1 is one of the most widely studied genes associated with hypertension-induced kidney damage. APOL L1 is a lytic factor in human serum that protects against trypanosomes that cause sleeping sickness [11]. Two disease-causing genetic variants of APOL L that arose in African populations conferred enhanced protection against virulent trypanosome subspecies. In 2010, Giulio Genovese and colleagues reported that two independent G1 and G2 sequence variants in APOL L1 were associated with European patients. The latter carries the wild-type APOL L1 gene G0 [19]. They also investigated the effect of APOL L1 variants on the progression of hypertension-induced CKD in large cohorts of black and white patients with hypertension-induced CKD [33]. They reported a significant association between G1 and G2 risk variants in APOL L1 and higher rates of ESRD and CKD in black patients [26].

Hypertensive kidney injury associated with APOL L1 variants may include alteration in podocyte function. Although the underlying mechanisms remain to be determined, APOL L1 variants can create pores in cell membranes and impair podocyte function in much the same way as trypanosome lysis. Flattening of the foot processes and glomerulosclerosis have been found in transgenic mice that contain podocyte-specific APOL L1 risk alleles, which may be associated with changes in endosomal transport and autophagy in podocytes. In addition, APOL L1 increases the vulnerability of podocytes to damage in response to oxidative stress associated with hypertension. It was also shown

Conclusions. Timely diagnosis is a key element in the diagnosis and prevention of end-stage renal disease. The discovery of a strong association between APOL L1 and CKD in populations of recent African ancestry demonstrates that non-diabetic nephropathy with low proteinuria is often inherited in this population and causes a secondary increase in blood pressure. Many studies in populations of different ages, with various kidney and systemic diseases, as well as in population cohorts support this conclusion. It remains important to recognize that intensive blood pressure control, including high-dose RAAS blockade, does not slow progression or prevent eGFR decline in individuals with hypertension, CKD, and subnephrotic proteinuria.

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