Genetics in Kidney Diseases

Böbrek Hastalıklarında Genetik

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ABSTRACT

During the last two decades, developments in molecular biology and genetics have caused a revolution in medicine. Advances in gene cloning, gene mapping, and mutation analysis have contributed to an incredible amount of new information regarding the biological and pathophysiological basis for human diseases including kidney diseases. In 'monogenic diseases", a mutation of a single gene is sufficient to cause the disease. Conversely, in polygenic disorders, mutations of multiple genes are necessary to result in a disease. Progressive chronic kidney disease remains a major challenge in nephrology. Genome-wide expression analysis of disease processes has been pioneered in onco logy, and molecular approaches have now been included in the initial diagnosis. Although we still have difficulties in sample analyses of the kidneys, some of the molecular diagnostic approaches are now used routinely in nephrology as well. In this review, recent developments in the field of the molecular bases of kidney diseases will be addressed. *(Gazi Med J 2011; 22: 118-23)*

Key Words: Nephrology, genetics, hereditary, molecular, childhood

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ÖZET

Son yıllarda genetik ve moleküler biyolojideki gelişmeler tıpta bir devrim niteliğindedir. Buna paralel olarak böbrek hastalıklarının moleküler temelleri ve dolayısıyla hastalık patogenezleri daha iyi anlaşılmaya başlanmıştır. Bu gelişmeler ileride nefrolojide yeni, daha kullanışlı tanısal belirteçlerin ve daha etkili tedavi hedeflerinin tanımlanmasına olanak sağlayacaktır. İlk kez onkolojide tüm genomu ilgilendiren ekspresyon analizleri yapılmış ve günümüzde birçok onkolojik malignensilerde moleküler yaklaşımlar tanı, sınıflandırma, ve tedavinin izleminde rutin olarak kullanılmaya başlanmıştır. Günümüzde moleküler tanı yaklaşımları nefrolojide de rutin olarak kullanılmaktadır. Ancak böbrek hastalığı olan hastaların moleküler karakterizasyonu ve böbreklerdeki hücresel heterojenite nedeniyle oldukça komplekstir. Böbrek biyopsi örneğinin de küçük boyutlu olması böbrek hastalıklarının doku düzeyinde analizine ilave bir güçlük katmaktadır. Bu nedenle böbrek hastalıklarıyla ilişkili biyolojik sıvılarda non-invazif analiz yöntemlerinin geliştirilmesine gereksinim vardır. Bu yazıda, böbrek hastalıklarının moleküler temelleriyle ilgili son gelişmeler üzerinde durulacaktır. *(Gazi Med J 2011; 22: 118-23)*

Anahtar Sözcükler: Nefroloji, herediter, genetik, moleküler, çocukluk çağı

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INTRODUCTION

Advances in gene cloning, gene mapping, and mutation analysis have contributed to an increased amount of new information regarding the biological and pathophysiological basis of human diseases. The degree of genetic causality varies with the mode of inheritance (MOI). There is strong genotype-phenotype correlation in monogenic recessive diseases, where the disease phenotype is determined by the single-gene causative mutation. Recessive diseases usually manifest prenatally, in childhood or in adolescence. Dominant diseases manifest typically in adults (e.g., in autosomal dominant polycystic kidney disease). Their genotype

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phenotype correlation is slightly reduced when compared to recessive diseases, because of the incomplete penetrance and different expressivity (Table 1).

In nephrology, a wide range of clinical phenotypes can now be explained at a molecular level.

Most of the information comes from the defined genes that are responsible for a variety of inherited syndromes, including streoid resistant nephrotic syndrome, polycystic kidney disease, cystinuria, Alport's syndrome, Bartter's syndrome (1).

MENDELIAN DISORDERS OF THE KIDNEY

A single gene defect causes a wide variety of renal diseases. Some of the inherited disorders with primary renal involvement extracted from the extensive Online Mendelian Inheritance in Man (OMIM) database are listed in Table 2. Single-gene defects are transmitted in families as autosomal dominant, autosomal recessive, or X-linked traits. There is a wide range of clinical expression, ranging from benign metabolic disorders, diseases of moderate morbidity such as hypertension and nephrolithiasis, to life-threatening diseases associated with end-stage renal disease (ESRD. Although many of these inherited diseases are manifest in childhood, an important portion occur later in life. Recognizing these and other late-onset disorders by molecular genetics will offer an opportunity for presymptomatic diagnoses or to predict development of the disease and to intervene therapeutically (2-4).

MOLECULAR DIAGNOSTICS

The information of a molecular genetic basis for a disease in a patient has great potential clinical utility. This information can be useful for diagnostic and as well as prognostic evaluations and may be important for specific therapies. Mutation analysis is usually performed by PCR of exons followed by direct exon sequencing, as it is estimated that about 85% of all disease-causing mutations in single-gene disorders are positioned within a coding exon (4, 5).

Glomerular Diseases

The major diagnostic sign of glomerular diseases is proteinuria and glomerular basement membrane (GBM) and podocytes are the main actors in glomerular function.

Podocytes

Recent studies showed the podocyte as probably the central player in the control of glomerular filtration. Specifically, the cell to cell interaction between adjacent podocyte foot processes, the slit diaphragm, which dynamically controls foot process architecture are the major actors. Key genes that have been identified from the study of inherited nephrotic syndrome (NS) include those encoding nephrin, podocin, TRPC6 and α -actinin 4 . It is now possible to identify genetic causes underlying a proportion of NS presenting at any age, and this review aims to help describe the genetics of NS according to age of presentation, and provide information on known mutations (6, 7).

Recessive mutations in *NPHS1* (nephrin) cause congenital nephrotic syndrome with an onset within 90 days of life (5). Mutations of *NPHS2* (podocin) (5) cause 10-30% of all non-familial childhood steroid resistant nephrotic syndome (SRNS) cases (Table 2) (2). Most of monogenic forms of SRNS lead to chronic kidney disease (CKD) and are resistant to steroid treatment (6). There is a strong correlation between causative gene mutations and the age of onset of FSGS or CKD. For instance, mutations in *NPHS1* (nephrin), *NPHS2* (podocin), *LAMB2* (laminin-β2), and *PLCE1* (phospholipase C epsilon 1) cause childhood onset SRNS, whereas the rare mutations in dominant genes, including *actinin-α4* (*ACTN4*) and *TRPC6* lead to adult onset disease (6-14) with rare exceptions (Table 2). We can exemplify this by the fact that 85% of all SRNS that manifests in the first 3-6 months of life and 66% of all SRNS manifesting in the first year of life are caused by mutations in one of only four genes, *NPHS1*, *NPHS2*, *LAMB2*, or *WT1* (10) (14).

Childhood Onset

NPHS1

Nephrin is probably the most important component of the slit diaphragm and is responsible for the autosomal recessive condition, congenital NS (CNS) of the Finnish type. The disease is common in Finland (incidence of 1: 10,000) and it often presents in utero with foetal growth retardation, polyhydramnios and massive proteinuria at birth. Common mutations are the Fin major (a frameshift mutation in exon 2 resulting in a truncated protein) and Fin minor (a nonsense mutation in exon 26 also resulting in a truncated protein) (7).

NPHS2

Podocin was originally thought to represent a cause for FSGS in older children, especially in familial forms (6). In the original description, one particular mutation (R138Q) was noted to be the most common one (1:3 of all patients with a mutation) (14). Interestingly, the incidence of NPHS2 mutations in African-American children with FSGS appears much lower, despite the fact that this group has a higher incidence of FSGS overall with a poorer outcome (14).

Table 1. Power of molecular genetic diagnostics

	Monogenic		Polygenic
	Recessive	Dominant	
Genetic causality	Strong	Intermediate	Weak
Penetrance	Full	Sometimes incomplete	Weak
Predictive power of mutation analysis	Almost 100%	Strong	Weak
Age of onset	Fetus, child, adolescent	Adult adolescent,	Adult
Molecular genetic approaches	Direct exon sequencing of known disease genes	Direct exon sequencing of known disease genes	Only assignment of relative risk possible
Frequency	<1:40,000 (rare)	<1:1,000 (rare)	<1:5 (frequent)

Table 2. Inherited diseases with kidney involvement

Disease	Protein	Gene/Locus
Primary glomerular disease		
Alport's syndrome, X-linked	Type IV collagen, α5	COL4A5, Xq22
Alport's syndrome, autosomal	Type IV collagen, α3	COL4A3, 2q26-q37
Recessive	Type IV collagen, α4	COL4A4, 2q26-q37
Congenital nephrosis I (Finnish type)	Nephrin NPHN,	19q13
Focal segmental glomerulosclerosis I	?	19q13
Focal segmental glomerulosclerosis II	?	11q21-q22, ? other
Nail patella syndrome	LIM-homeodomain protein	LMX1B, 9q34.1
Familial mesangial sclerosis	Wilms' tumor suppressor 1	WT1, 11p13
Familial IgA nephropathy	?	?
Cystic renal diseases		
Polycystic kidney disease 1	Polycystin I PKD1,	16p13.3
Polycystic kidney disease 2	Polycystin II PKD2,	4q21-q23
Infantile severe polycystic kidney disease with tuberous sclerosis	Polycystin I and tuberin	PKD1 and TSC2 16p13.3
Autosomal recessive polycystic kidney disease	?	6p21.1-p12
Familial juvenile nephronophthisis1	MAL-like protein NPHP1,	2q13
Renal tubular diseases		
Distal renal tubular acidosis	Anion exchanger 1	SLC4A1, 17q21-q22
Nephrogenic diabetes insipidus (X-linked)	Vasopressin receptor type 2	AVPR2, Xq28
Nephrogenic diabetes insipidus (autosomal)	Aquaporin 2 water channel	AQP2, 12q13
Bartter's syndrome type 1	Na-K-2Cl cotransporter	SLC12A1, 15q15-q21
Bartter's syndrome type 2	ROMK K channel	KCNJ1, 11q24
Bartter's syndrome type 3	Cl channel,	ClC-Kb CLCNKB, 1p36
Gitelman's syndrome	Na-Cl cotransporter	SLC12A3, 16q13
Cystinuria, type I	Cystine transporter	SLC3A1, 2p16.3
Cystinuria, non–type I	Cystine transporter	SLC7A9, 19q13.1

WT1

WT1 is a podocyte transcription factor associated with Wilms' tumours and the WAGR (Wilms tumour, Aniridia, Genitourinary malformation and mental retardation). Originally, it was thought that WT1 represents a small cohort of patients, but there are now many phenotypes which were identified. A WT1 mutation in the zinc finger (DNA binding) region causes the Denys Drash syndrome, which comprises diffuse mesangial sclerosis (DMS) and extrarenal manifestations (pseudohermaphroditism and Wilms' tumour) (5, 14). The renal phenotype is severe and usually causes the early onset of disease which typically shows non-responsiveness to steroids and immunosuppression and rapidly progresses to end stage kidney disease (ESRD).

NPHS3 (PLCe1)

Hinkes et al. (10) described truncating mutations in PLCe1, leading to isolated DMS and missense non-truncating mutations leading to FSGS.

Adult Onset

ACTN4

Although rare, the most common genes involved in SRNS with adult onset include ACTN4. It is an actin-binding and cross-linking protein integral to the podocyte cytoskeletal structure. Originally it was identified in two pedigrees with an autosomal dominant FSGS, causing an adolescent or young adult onset NS with slow progression to end-stage renal failure in later life. Interestingly there are now case reports describing ACTN4 mutations in childhood-onset disease (6).

TRPC6

TRPC6 was first described in a large pedigree, again causing an autosomal dominant FSGS. Although general presentation was in the 3rd or 4th decade, the youngest patient was 17 years of age. Unlike the previously mentioned ACTN4 mutations, the disease progresses rapidly to end-stage renal failure within 10 years (14).

Table 3. The leading diagnostic features of renal calculi or nephrocalcinosis

Nephrolithiasis	MOI	Characteristic signsand features	*Gene symbol*, gene product
Cystinuria, type	AR	Cystin calculi	*CSNU1*, SLC3A1 amino acid transporter
Cystinuria, non-type 1	AR	Cystin calculi	*SLC7A9*, amino acid transporter
Primary hyperoxaluria type 1	AR	NL, CKD	*AGXT*, Ala-glyoxylate aminotransferase
Primary hyperoxaluria type 2	AR	NL	*GRHPR*, glyoxylate reductase
Xanthinuria	AR	NL, xanthine calculi	*XHD*, xanthin dehydrogenase
Distal renal tubular acidosis	AD	NL, ricketts	*SLC4A1*, RTA
Dent disease	XR	NL, NC, renal Fanconi syndrome	*CLCN5*, renal Cl-Channel
Lysinuric protein intolerance	AD	NL, phosphate wasting,osteopenia	*SLC9A3R1*, NHERF1

AD: autosomal dominant, AR: autosomal recessive, NC: nephrocalcinosis, NL: nephrolithiasis, RTA: renal tubular acidosis, XR: X-linked recessive

Table 4. Complex genetic traits involving the kidney

Essential hypertension
Susceptibility to ESRD
Diabetic nephropathy
Hypertensive nephrosclerosis
Susceptibility to acute renal injury
Renal neoplasms
Nephrolithiasis
Acquired renal cystic disease
Immune-mediated renal disease
Lupus nephritis
IgA nephropathy

CD2AP

There have been only a very limited number of case reports, and the phenotype is variable. The first description was in adults with a heterozygous mutation in exon 7, but the next was a homozygous mutation in exon 18 in a child with infantile onset and rapid progression to end stage (14).

Glomerular Basement Membrane

The glomerular basement membrane (GBM) is a specialized form of basement membrane that has a major role in the maintenance of the glomerular filtration barrier. Similar to all basement membranes, it contains four main components: type IV collagen, laminin, nidogen, and heparan sulfate proteoglycans. Different isoforms of these large molecules are produced. These isoforms have a tissue-specific distribution; in the mature GBM, the major type IV collagen molecule is the α3α4α5 (IV) isoform, associated with laminin-521 (α5β2γ1), nidogen and agrin heparan sulfate proteoglycans. Mutations in type IV collagen or laminin genes have been shown to be associated with hereditary glomerular diseases (15, 16).

Alport Syndrome

Alport syndrome is a widely known disorder of GBM and is characterized by the familial occurrence of progressive hematuric nephritis and hearing loss. Alport syndrome affects 0.3-2.3% of all patients who develop end stage renal disease (ESRD) in Europe, and the US. Ultrastructural studies have shown that the descriptive lesion of Alport syndrome involves the GBM. The ultrastructural picture is characterized by thickening of the GBM (up to 800-1,200 nm) with splitting and fragmentation of the lamina densa into several strands, a 'basket weave' pattern is formed with irregular inner and outer contours. The genetics and underlying causes of Alport syndrome remained problematic until the identification of the *COL4A5* gene encoding the α5 type IV collagen chain, and detection of the first *COL4A5* mutations in the most frequent, X-linked form of the disease. The genes encoding the α3 (IV) and α4 (IV) chains were then cloned, leading to identification of the first mutations in *COL4A3* and *COL4A4* in the autosomal Alport syndrome. After these detailed investigations, these major findings showed that Alport syndrome was a disorder of type IV collagen, and was heterogeneous at the genetic level (17, 18).

X linked dominant Alport syndrome

Alport syndrome is transmitted as an X-linked dominant trait in about 85% of affected families of European origin. This mode of transmission is characterized by a higher rate of disease severity in males than in females and the absence of father-to-son transmission. Since the identification of *COL4A5*, 7, 8, more than 300 mutations have been reported in this gene. Mutations occur throughout the gene and each affected family may be characterized by its own mutation. Major changes in *COL4A5*, including deletions of various locations, insertions, or complex rearrangements, have been identified in 5-20% of affected families. Single base changes account for about 40% of small mutations and most of them are missense mutations in glycine codons that disrupt the Gly-X-Y repeats in the collagenous domain of *COL4A5* (17, 18).

Autosomal recessive Alport syndrome

Alport syndrome is transmitted as an autosomal recessive trait in about 10-15% of families carrying the disease. Autosomal recessive Alport syndrome is usually severe; nephritis progresses to early-onset ESRD, hearing impairment affects the majority of patients, and ocular lesions may or may not be present. The clinical and morphological features are identical in the autosomal recessive and X-linked forms. Homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* have been detected in several kindreds (18).

Autosomal dominant Alport syndrome

Autosomal dominant inheritance of Alport syndrome is characterized by male-to-male transmission. Progression to ESRD and

hearing defect are not always seen and usually occur after 50 years of age; no ocular involvement has been reported. The clinical phenotype is variable and milder than that of the X-linked dominant form. Thickening and splitting of the GBM, or diffuse thinning, have been observed, but the distribution of α (IV) chains is normal. Mutations in the *COL4A3* or *COL4A4* genes have been reported in six unrelated families (18).

Cystic Disease

Polycystic Kidney Disease (PKD) represents a diverse collection of disorders of the tubules of the kidney, where healthy renal tissue is progressively replaced by fluid-filled cysts. Extra-renal manifestations are also seen in PKD, including hypertension, biliary ectasia and fibrosis leading to portal hypertension, hepatic cysts, and intra-cranial aneurysms. Autosomal dominant PKD (ADPKD) is the most common form, with a symptomatic onset usually during the third and fourth decades of life, although childhood onset has been documented (19, 20). Autosomal recessive PKD (ARPKD) is rare, with symptoms often beginning in utero or during the neonatal period.

The two genes mutated in ADPKD, *PKD1* and *PKD2*, encode polycystin 1 and polycystin 2, which play a role in the maintenance of renal tubular cell differentiation (Table 2) (5, 19). Molecular genetic diagnostics have been technically very difficult, but recently up to 90% of cases with ADPKD can now be diagnosed, which is very helpful for clinical decision making, especially regarding living related donor transplantation (18). Autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilateral renal cystic enlargement that may start *in utero*. Depending on the severity of the two recessive mutations in the causative *PKHD1* gene, CKD develops directly postnatally, in childhood or in adolescence (Table 2).

Nephronophthisis (NPHP) is characterized by involvement of the corticomedullary border of the kidneys by cysts and the kidney size is usually normal or reduced. It is the most frequent genetic cause of CKD in the first three decades of life (19-21). CKD develops by the second decade. Mutations in nine different recessive genes (*NPHP1-NPHP9*) have been identified as causing NPHP (Table 2) (19-22). It can be associated with cerebellar vermis aplasia (Joubert syndrome, JBTS), liver fibrosis, and retinal degeneration (Senior-Loken syndrome, SLSN).

Tubular Disorders

Renal tubules are responsible for reabsorption of water and solutes from the glomerular filtrate. An increasing number of tubulopathies are currently being recognized as caused by single-gene mutations. In renal tubulopathies the primary genetic defect causes loss of function of a specific renal transport protein or signaling molecule. As certain transport systems are expressed in specific tubule segments, clinical and diagnostic features allow focusing genetic diagnosis on genes expressed in those tubule segments. For some diseases, such as Bartter's syndrome, similar disease phenotypes may be caused by mutations in different genes (5, 23, 24).

Functional disturbances of different tubule segments cause the various defects of tubular reabsorption (Table 2). Proximal tubular defects cause glucosuria, phosphaturia, aminoaciduria and/or proximal renal tubular acidosis (RTA) (25-29). This combination of features is known as renal Fanconi syndrome. Sodium reabsorption dysfunctionin the thick ascending limb of Henle's loop causes Bartter's syndrome, renal salt loss and secondary hypokalemic metabolic alkalosis. Defects of the distal convoluted tubule cause Gitelman syndrome and other forms of hypomagnesemia (25-27). Tubulopathies of the collecting duct impair reabsorption of sodium, potassium and water, causes hyperkalemia, salt loss, polyuria, and acidosis. Mutations in the aquaporin-2 water channel AQP2 (62) results in recessive nephrogenic diabetes insipidus (NDI), and mutations in the vasopressin-2-receptor cause Xlinked NDI (29).

Nephrolithiasis

Nephrolithiasis is one of the leading causes of CKD in our country. Multiple single-gene causes of nephrolithiasis have been identified (Table 3) (5). Most of the single-gene causes represent rare abnormalities of specific renal tubular transport channels. Whether "mild" mutations in these genes may represent alleles conveying an increased risk of nephrolithiasis is currently unclear (30). The genotype- phenotype relation also differs in some familials within individuals who carry the same mutations. In our previous studies, we found that ApaI AA genotype of the VDR gene is associated with AH and the frequency of ApaI AA genotype was significantly higher in the children with calcium nephrolithiasis than the controls (31, 32). So we need to know more regarding the molecular genetics of nephrolithiasis.

COMPLEX GENETIC KIDNEY DISEASES

With the exception of Alport's syndrome, polycystic kidney disease, cystinuria, and a few others, single-gene disorders with primary renal involvement are rare. On the other hand, a number of common disorders affecting the kidney form complex interactions between genetic predisposition and environmental factors (Table 4). Such genetic complexity, also known as polygenic disorders, must be considered separately from diseases caused by defects in single genes. Common diseases such as essential hypertension, renal cancer, and some forms of nephrolithiasis occur in patients who have a unique genetic susceptibility that may come from subtle variations in multiple genes. Additionally, genetic susceptibility should not be necessarily associated with a high likelihood of disease occurrence.

FUTURE OF GENETICS IN KIDNEY DISEASE

The most important feature of monogenic diseases is that the mutation in itself represents the primary cause (etiology) of the disease. This provides the following opportunities for diagnostics, follow up, therapy, and insights into pathogenesis: i) Molecular genetic diagnostics can help to avoid invasive procedures, e.g. the diagnosis of nephronophthisis can be made without the necessity for renal biopsy. ii) Prognostic outcomes can be defined for specific mutations, e.g. in mutations of *PKD1* or *PKD2*, which cause earlier or later onset of autosomal dominant polycystic kidney disease, respectively. iii) Prenatal diagnosis is possible. iv) Subgroups of diseases may be classified for therapy options, e.g. in mutations in *NPHS2*, which reveals resistance to steroid treatment in the nephrotic syndrome. The nature of inherited diseases makes them theoretically susceptible to therapies aimed at correcting or replacing the defective gene. In addition to the treatment of classical inherited diseases, in future, genetic therapies may be initiated to modify disease susceptibility in complex diseases such as hypertension and the progression to ESRD, and modulate the immune response in transplant rejection, or other immune-mediated renal diseases.

In summary, novel molecular genetic techniques will rapidly provide novel insights into kidney diseases, especially regarding their diagnosis, classification, and development of new therapeutics.

Conflict of Interest

No conflict of interest was declared by the authors.

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