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Review

NOVEL GENETIC ASPECTS OF CONGENITAL ANOMALIES OF KIDNEY AND URINARY TRACT

STEFANIE WEBER*

Purpose of the review. Congenital anomalies of the kidney and urinary tract (CAKUT) are among the most frequent organ malformations. They are a relevant cause of chronic renal failure in children. Besides isolated forms of CAKUT, more than 500 syndromes have been described that are characterized by combined defects of the kidney and other organ systems. Familial aggregation of renal malformations in approximatively 10% of patients suggests that genetic events might be involved. Modifying effects due to missense mutations in additional developmental genes seem to enhance the phenotypic variability in affected families. In these families, genetic counseling can be difficult. In contrast, in patients with defined autosomal dominant disease, genetic counseling is of high clinical relevance, also with respect to additional extrarenal symptoms.

Recent findings: Due to (1) the development of numerous genetic knock-out mouse models, (2) the identification of specific renal developmental genes and (3) the application of novel sequencing techniques of the human genome our understanding of kidney organogenesis has largely improved during the very recent years.

Summary: This review will focus on important genetic factors that influence nephrogenesis and high lightening important human disorders that are associated with anomalies of kidneys, proximal and distal urinary tract.

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are a frequent cause of renal insufficiency and end-stage renal disease in children. They are observed in 3-6/1000 pregnancies and belong to the most frequent congenital organ malformations in humans (1). Due to the elevated frequency of routinely performed ultrasound examinations in the pre- and postnatal period the detection rate of renal abnormalities is rising steadily. The term CAKUT comprises malformations of the kidney (renal agenesis, hypoplasia, dysplasia, double kidneys) associated with anomalies of the ureter (obstructive as seen in proximal ureteral stenosis, or refluxive). Some authors also assign anomalies of the bladder and urethra (e.g. posterior urethral valves) to the CAKUT spectrum.

Besides isolated cases of CAKUT, combined malformations are observed as part of a complex syndromal phenotype. More than 500 syndromes have been described involving renal or urinary anomalies (e.g. Townes-Brock syndrome, Kallmann syndrome and others).

The majority of patients manifesting with CAKUT are sporadic cases but also familiar forms have been described suggesting that the pathogenesis is influenced by genetic factors. A positive family history for malformations of the kidney is observed in approximatively 10% of index cases. A large number of monogenic *knock-out* mouse models have been developed with offspring manifesting a phenotypic spectrum which mimics the human CAKUT complex (reviewed in (2)). These observations lead to the assumption that monogenic influences might be effective in human CAKUT patients. Besides numerous candidate genes discussed to be relevant for manifestation of CAKUT in children, a number of known genes have been identified in recent years to be associated with disorders of renal development (Table 1). New CAKUT associated genes are constantly identified, in general with a low mutation detection rate for each gene. In this review, only a subset of these genes will be discussed.

Novel hypotheses have been developed to better understand the pathogenesis of CAKUT, based on aspects of early kidney development. Many basic researchers interested in gene networks and signaling pathways have established important aspects of the regulation of kidney organogenesis.

Kidneys and ureters are derivates of the intermediate mesoderm. The final kidney (metanephros) forms in the human embryo out of two different mesodermal tissues: the metanephric mesenchyme and the metanephric duct

*University Children's Hospital Essen
Pediatrics II

Address:
Stefanie Weber, M.D.
Pediatrics II, University Children's Hospital Essen
Hufelandstrasse 55, 45122 Essen, Germany
E-mail: stefanie.weber@uk-essen.de

Table 1.
Genetically determined disorders associated with anomalies of kidneys and urinary tract (CAKUT) (selection)

Gene	Chromosome	Inheritance	Clinical spectrum
HNF1β	17q12	ad	Renal hypodysplasia, frequently with renal cysts; Rrenal Cyst and Diabetes Syndrome (RCAD), MODY 5
GDNF	5p13.1-p12	ad	Hirschsprung disease/CAKUT
RET	10q11.2	ad	Hirschsprung disease/CAKUT
PAX2	10q24.3-q25.1	ad	Renal coloboma syndrome (RCS), Renal hypodysplasia
EYA1	8q13.3	ad	Branchiootorenal syndrome (BOR)
SIX1	14q23	ad	Branchiootorenal syndrome (BOR)
SIX5	19q13.3	ad	Branchiootorenal syndrome (BOR)
AGT	1q42-q43	ar	Renal tubular dysgenesis (RTD)
REN	1q32	ar	Renal tubular dysgenesis (RTD)
ACE	17q23	ar	Renal tubular dysgenesis (RTD)
AGTR1	3q21-q25	ar	Renal tubular dysgenesis (RTD)
BMP4	14q22-q23	(ad)	Renal hypodysplasia/agenesis
SIX2	2p16-p15	(ad)	Renal hypodysplasia
UPIIIA	22q13.31	ad	Renal hypodysplasia
FRAS1	4q21.21	ad	CAKUT
FREM1	9p22.3	ad	CAKUT
SALL1	16q12.1	ad	Townes-Brocks syndrome (TBS) (digital and kidney anomalies, imperforate anus, inner ear deafness)
ROBO2	3p12.3	ad	Vesicoureteral reflux (VUR)/CAKUT
SOX17	8q11.23	ad	Proximal ureteral junction obstruction (PUJO)/VUR
HPSE2	10q24.2	ar	Urofacial syndrome (UFS)/Ochoa syndrome with dysmorphic, poorly-emptying bladder
CHRM3	1q43	ar	Functional bladder outlet obstruction/Prune-belly syndrome (PBS)

Abbreviation: ad: autosomal dominant, ar: autosomal recessive

deriving from the Wolffian duct. During growth of the metanephric duct into the metanephric mesenchyme reciprocal inductive signals are secreted by both tissue types, enabling the development and differentiation of the definitive structures of the kidneys.

These interactions are most crucial for normal development of both, kidneys and urinary tract. Piscione and Rosenblum have summarized in their important review these aspects of molecular control of renal branching morphogenesis shedding new light on an old theory of combined anomalies of kidney and urinary tract: the *budding hypothesis* (2).

Budding-Hypothesis

Following the observation of a correlation between site of insertion of the ureter into the bladder and degree of renal hypo- or dysplasia with associated anomalies of the ureter in human embryos with double kidneys, Mackie and Stevens hypothesized 1975 that a single event might be the underlying cause of this malformation complex: hereafter, an ectopia of the ureteric bud is responsible for both: an ectopic opening of the ureter into the bladder and hypo- or dysplasia of the kidneys (3). This has been explained by the fact that the ectopic ureteric bud touches only sparsely populated metanephrogenic mesenchyme which is accompanied by misinduction of kidney development. (Figure 1A): Cranial budding of the ureter will lead to caudal positioning of the opening into the bladder while caudal budding will be associated with canial and lateral opening into the bladder (due to caudal movement of the developing kidney during organogenesis). Caudal opening of the ureter into the bladder is frequently associated with distal ureteric obstruction, cranial opening with insufficient and refluxive opening (causing vesicoureteral reflux, VUR). Therefore, the defect in urinary transport is not the cause of kidney dysplasia but - together with the latter - the consequence of impaired budding of the ureter and misinduction of kidney tissue (2, 4). Today, scientific advances have lead to the identification of genes and signaling molecules (e.g. Ret, Gdnf, Pax2, Bmp4 and many others) involved in the regulation of budding, branching and induction of kidney formation, strongly supporting the important theory of Mackie and Stevens (Figure 1B).

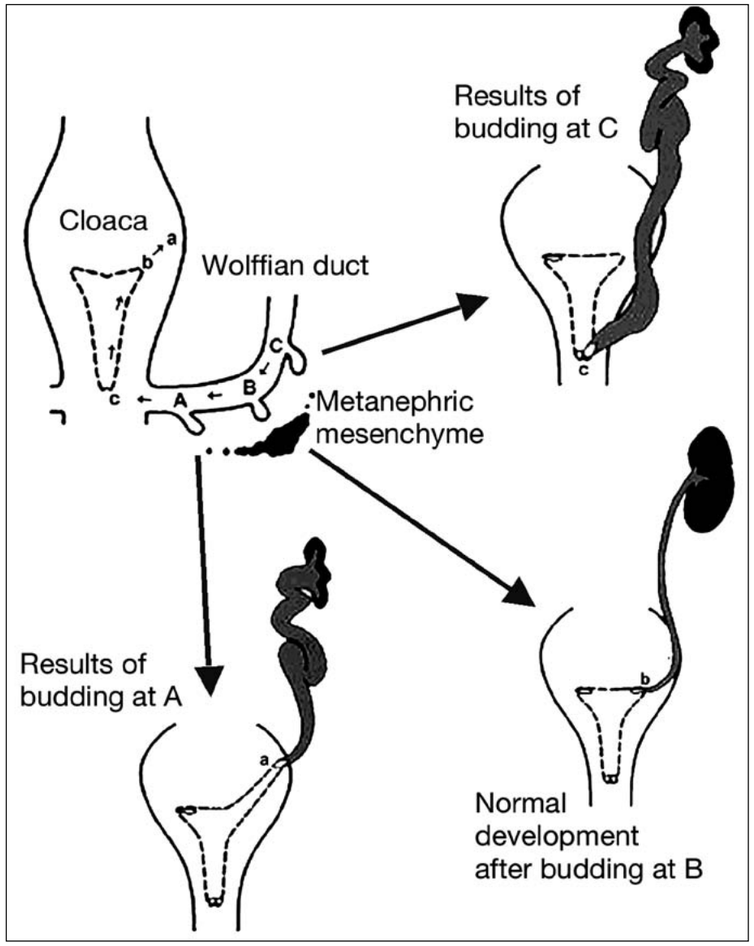

Figure 1A.
The budding hypothesis: Ectopic budding of the ureter (A, C) causes ectopia of the ureteral opening into the bladder (a, c) with consecutive reflux or obstruction and dysplasia of the renal tissue (Figure modified after (4)).

The action of Gdnf (*glial-cell-line-derived neurotrophic factor*) plays a central role in initiating the budding of the ureter. Gdnf binds to its receptor Ret, which is expressed in the ureteric bud. The expression of Gdnf itself is regulated by complex genetic cascades involving (among many others) PAX2, EYA1 and members of the SIX gene family (5). The site of budding is controlled by a number of inhibitors, one important inhibitory protein being Bmp4: budding does only occur where Bmp4 is not expressed (6).

Of note, numerous renal developmental genes are not only important for nephrogenesis but also for the development of other organs (e.g. eyes, inner ear, brain). Based on their specific organ pattern of expression different extrarenal symptoms can be explained (e.g. retinal anomalies or inner ear deafness).

Other scientists, however, believe that malformations of the kidneys observed in CAKUT are a consequence of intrauterine obstruction of the urinary tract. Following these authors, mechanical obstruction and the associated rise in intraluminal and intrarenal pressure are the key events for establishing kidney dysplasia. In addition to physical pressure, the altered secretion of growth factors and infiltration of macrophages induces enhanced apoptosis and dysplasia of the renal tissue. These aspects of urinary tract obstructions have been reviewed by Chevalier (7). This physical model of renal damage induced by urinary obstruction underscores the importance of surgical interventions in posterior urethral valves, distal and proximal ureteral stenosis and refluxive nephropathy to reconstitute normal urinary flow. Taken both theories together (budding hypothesis and model of obstruction) it seems reasonable to believe that obstructive changes cause further kidney damage after initial maldevelopment due to impaired budding. In the following section some important recent genetic findings will be reviewed.

Renal Cysts and Diabetes syndrome

One of the most important genes involved in kidney dysplasia is HNF1β encoding *hepatocyte nuclear factor*-1β which is a transcription factor expressed in many different tissues during embryogenesis (e.g. kidney, liver, pancreas). Dominant mutations in HNF1β are associated with Renal Cysts and Diabetes syndrome (RCAD), characterized by renal malformations (especially cystic dysplasia of the kidney) and maturity onset diabetes of the young (MODY type 5) (8). In some RCAD patients, elevated serum levels of liver enzymes and uremic acid have been described. An important study published in 2006 by Ulinski and colleagues, reported that mutations in HNF1β are also identified with high frequency in children with isolated renal malformations, the majority of them pre-

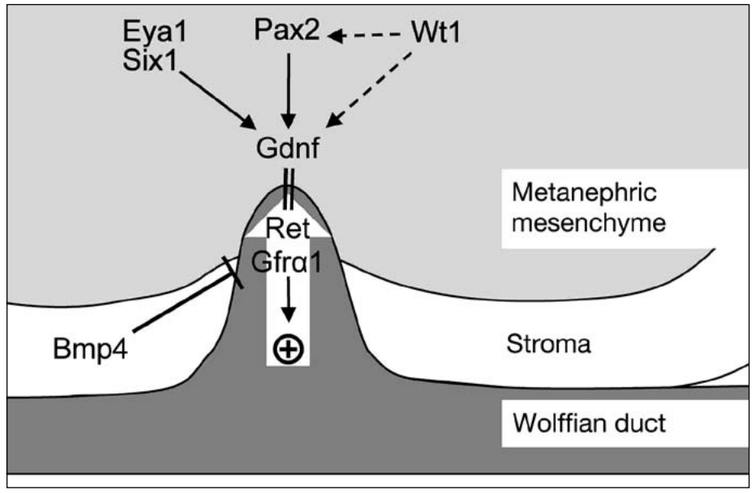

Figure 1B.
Budding of the ureter into the metanephric mesenchyme during early kidney development (Figure kindly provided by Raphael Schild, University Children's Hospital Hamburg, Germany).

senting with cystic hypo- or dysplasia of the kidney (9). Similar results have been observed in a large European multicenter study. Here, HNF1β mutations were identified in 25% of all patients with cystic lesions of the kidney but in only 3% of children with noncystic lesions (10). Of note, autosomal dominant or recessive polycystic kidney disease (ADPKD and ARPKD) should not be confounded with renal cystic hypodysplasia as they have a different genetic basis, renal histology and clinical course. Interestingly, a subset of patients with HNF1β mutations presents with significantly lowered levels of serum magnesium and renal magnesium loss, a phenomenon most probably explained by transcriptional regulation of renal magnesium transport proteins by HNF1β (11).

Following these recent studies, many authors have concluded that a systematic screening of HNF1β in patients with cystic hypodysplasia of the kidneys seems justified and clinically relevant, especially with respect to late-onset manifestation of extrarenal symptoms including diabetes mellitus, hyperuricemia, and elevated liver enzymes. The dominant mode of inheritance is important for genetic counseling of the patients and their families.

Hirschsprung disease with associated renal anomalies

Many renal developmental genes are directly or indirectly involved in regulating the action of Gdnf. Gdnf is expressed in the metanephrogenic mesenchyme and constitutes an important signal for the induction of ureteric budding and further growth and branching of the ureter (12, 13). For these actions Gdnf binds to its receptor Ret, expressed in the ureteric bud. The action of Gdnf is directly inhibited by Bmp4 (see below). Interestingly, dominant mutations in human RET have been identified in patients with isolated Hirschsprung disease (intestinal aganglionosis) (14), but also in individuals with isolated CAKUT (15). Some carriers of RET or GDNF mutations present with both Hirschsprung disease and renal anomalies (16).

Recently, a recurrent microdeletion at chromosome 16p11.2 has been associated with CAKUT and Hirschsprung disease in three unrelated boys - with SH2B1 located in the overlapping chromosomal region, encoding an adaptor protein which has been implicated in the enhancement of Ret activity (17).

Renal Coloboma Syndrome

Pax2 is a homoeobox transcription factor encoded by the gene PAX2 which directly regulates the action of Gdnf. Human mutations in PAX2 are associated with autosomal dominant renal coloboma syndrome (RCS) characterized by congenital anomalies of the kidney, coloboma of the optic nerve and hearing impairment in some cases (18). The renal (and urinary) phenotype comprises hypoplasia of the kidney, unilateral agenesis, multicystic-dysplastic kidneys (MCDK) and/or vesicoureteral reflux (VUR). End-stage renal disease (ESRD) occurs in almost 100% of individuals with PAX2 associated renal hypoplasia. The most common eye abnormalities are optic nerve disc dysplasia or cystic dilatations of the optic nerve posterior to the globe. Visual acuity is reduced in one or both eyes in 75% of affected individuals. In a European multicenter study PAX2 mutations were identified in 7 out of 100 CAKUT patients (10). In four affected children, hearing impairment and ocular anomalies have only been identified by careful clinical reevaluation after obtaining the results of genetic testing suggesting that early clinical examination of vision and hearing capability are advised in all CAKUT patients. The age at diagnosis of RCS is broad. A recent study identified PAX2 mutations in two fetuses presenting antenatally at 24 and 18 weeks of gestation with oligo-/anhydramnios, severe renal hypodysplasia and characteristic coloboma of the optic nerve (19). A second study analyzed PAX2 in pediatric and young adult transplant recipients with CAKUT as underlying diagnosis of ESRD and identified mutations in 2 out of 20 individuals (20). These authors suggest that PAX2 mutations should be sought for in all patients with severe malformations of the kidneys associated with ESRD.

Branchiootorenal syndrome

Branchiootorenal (BOR) syndrome is an autosomal dominant inherited disorder, characterized by variable combinations of anomalies of kidneys, branchial archs und external and inner ear. The prevalence of BOR syndrome is reported to be 1:40000 and seems responsible for 2% of cases of inner ear deafness in children. Mutations in EYA1, SIX1 and SIX5 have been identified as underlying cause with EYA1 being the major causative gene (21-24). Eya1 is a cofactor of Six1 and both are involved in regulating GDNF expression. Molecular genetic testing detects mutations in EYA1 in approximatively 40% of BOR cases (25). Mutations in SIX1 und SIX5 were only identified in a small subset of BOR families (26). The phenotypic variability of BOR is high. Some mutation carriers do not present a renal phenotype, but only branchial cysts or fistulae and anomalies of the ears (branchiootic syndrome (BOS)). BOR syndrome and BOS can also be seen within the same family.

Renal Tubular Dysgenesis

Autosomal recessive renal tubular dysgenesis (RTD) is a severe, most often lethal anomaly of kidney development, characterized by persistent fetal anuria and subsequent oligo/anhydramnion. Recessive mutations in different genes of the renin-angiotensin-system (RAS) have been identified to be causative in affected fetuses (27). These comprise mutations in AGT (encoding angiotensinogen), REN (renin), ACE (angiotensin converting enzyme) und AGTR1 (AT1 receptor), rendering RTD a genetically heterogenous disease. These findings impressively high lightened the role of the RAS for normal kidney development. Interestingly, heterozygous dominant mutations in REN were recently shown to result in early-onset hyperuricemia, anemia, and chronic kidney disease (28, 29).

BMP4

Bmp4 (*bone morphogenetic protein 4*) is a potent antagonist of Gdnf and plays a crucial role in many steps of human embryogenesis. One of its central actions is to inhibit ectopic budding of the ureter. Homozygous Bmp4 knockout mice die early in the antenatal period but heterozygous animals present with ectopic ureteric budding and a phenotypic spectrum highly comparable to the human CAKUT complex (6).

Human mutations in BMP4 and SIX2 were identified in a small number of pediatric CAKUT patients with renal hypodysplasia. Functional studies in zebrafish and cell culture models point to an alteration of Bmp4 protein function induced by these mutations (30, 31).

Other genes involved in CAKUT

Formerly, dominant human mutations have been identified in UPIIIA in a small number of patients with non-obstructive kidney hypodysplasia (32, 33). UPIIIA encodes for uroplakin IIIa, a member of a group of integral membrane proteins expressed at the surface of the urothelium of the bladder. In a very recent study applying massively parallel exon resequencing, heterozygous missense mutations were detected in 2 candidate genes (FRAS1 and FREM2) in patients with non-syndromic CAKUT (34). Recessive mutations in FRAS1 and FREM2 were known to cause Fraser (cryptophthalmus-syndactyly) syndrome, however, a phenotype in heterozygous carriers has not been described so far. In patients with Townes-Brocks syndrome (TBS) dominant mutations in SALL1 have been identified (35, 36). These patients are characterized by combined anomalies of hands and feet (e.g. triphalangeal thumbs), imperforate anus, inner ear deafness and malformation of the kidney and urinary tract (e.g. hypoplastic kidneys).

Ureteral anomalies

Vesicoureteral reflux (VUR) is the most common anomaly of the urinary tract observed in children, detected in up to 1% of infants after birth. Low-grade VUR frequently disappears during infancy but high-grade VUR persists and constitutes a risk factor for the development of urinary tract infections and loss of renal function. Many genetic studies have been performed aiming at identifying the genetic basis of familial VUR and a decade ago one significant gene locus has been identified on chromosome 1p13 (37). No causative gene has so far been localized within this critical interval. However, mutations were identified in a novel gene, ROBO2, in a small subset of patients with familial VUR/CAKUT in a subsequent study of Lu and colleagues (38).

Congenital pelvi-ureteric junction obstructions (PUJO) are identified in approximatively 0.3% of live born children. As mice inactivated for the teashirt3-gene (Tshz3) strikingly phenocopy human PUJO, the human homologue TSHZ3 represented an important candidate gene for this frequent anomaly observed in children. However, to date, no significant pathogenic mutations have been identified in human TSHZ3 (39). A different study reported a mutation in SOX17, a HMG-box transcription factor and Wnt signaling antagonist, in one patient with PUJO (40). In the same study, SOX17 mutations were also identified in 7 children with VUR.

Bladder anomalies with functional bladder outflow obstruction

Little is known about the genetic origin of malformations of the lower tract. Congenital bladder outflow obstruction (BOO) has several causes, the commonest being posterior urethral valves (PUV), with a high risk of developing chronic renal insufficiency (41). Recently, autosomal recessive mutations in HPSE2, encoding a heparanase inhibitor expressed in developing urinary tracts, were described in urofacial syndrome (UFS), also named Ochoa syndrome (42, 43). Typically, UFS patients present with a dysmorphic, poorly-emptying bladder in addition to a peculiar, "inverted" smile. After these initial descriptions, two confirmatory studies have been published very recently (44, 45). Also associated with congenital bladder dysfunction is prune belly syndrome (PBS). In its rare complete form, it comprises megacystis with disorganized detrusor muscle, cryptorchidism and thin abdominal musculature with overlying lax skin (resembling a "dried prune"). Very recently, a homozygous loss-of-function mutation in CHRM3 has been identified in five brothers with bladder dysfunction

and a PBS-like syndrome by exon capture and massively parallel sequencing (46). CHRM3 encodes the M3 subtype of muscarinic acetylcholine receptors, the major receptor mediating urinary bladder contraction upon micturition. Homozygous *Chrm3* mutant mice lacking M3 present with impaired bladder contractility and male mutant bladders are grossly distended *in vivo* (47). In human embryonic tissue, M3 was immunodetected in developing renal epithelia, bladder muscle and fetal urethral epithelia suggesting a role of M3 beyond its known contribution to detrusor contractions.

Detection of chromosomal microimbalances

Submicroscopic chromosomal anomalies can be identified today by applying DNA-chip-based technologies, especially in patients with complex syndromal malformations. In a recent study including patients with CAKUT and extrarenal symptoms submicroscopic deletions and duplications were identified in some individuals by applying comparative genome hybridization (array-CGH) techniques (48). The causative genes which are localized within the critical interval now remain to be identified.

New concepts of oligogenic inheritance

The sequencing of renal developmental genes in many CAKUT families has lead to the identification of non-Mendelian modi of inheritance in some pedigrees. Some mutation carriers apparently have normal kidneys on ultrasound and in other families the clinical variability is extremely broad. Modifying effects caused by mutations in additional developmental genes seem to augment the clinical variability in certain families. The identification of missense mutations in different developmental genes in single individuals has supported the idea that kidney development might only be disturbed if a threshold of additive mutations is overpassed (10). Modifying effects seem to play an important role in CAKUT manifestation and phenotypic variability. This complicates geentic counseling in affected families to a large extend because the risk of recurrence is incalculable and the severity of the phenotype in offsprings is unforeseen.

MicroRNAs as potential regulators of renal developmental genes

New concepts attribute the broad phenotypic variability of CAKUT not only to mutational but also to environmental and epigenetic factors. These epigenetic factors include among others DNA methylation, histone modifications and the action of miRNAs (49, 50). MiRNAs are small non-coding RNAs that act as regulators of gene expression through inhibition of their target mRNAs (51). Individual miRNAs are capable of targeting hundreds of gene targets and vice versa, any single mRNA can be inhibited by numerous miRNAs. Specific miRNAs were identified to be expressed during early kidney development and for a number of important genes involved in nephrogenesis a superordinate regulation by miRNAs has been revealed (50). These targets include Pax2, Hnf1β, TGF-β/Bmp signaling, Six/Eya1/Gdnf and Sox17 and Wnt signaling (50). Specific miRNAs have been demonstrated to be involved in the regulation of these genes (e.g. miR-562, miR17-92, miR125a, miR151 and others) and the gene products itself influence miRNA expression by feedback mechanisms. Overall, these results suggest, that miRNAs play a distict role in kidney development and that their misexpression contributes to the manifestation of kidney disease and/or phenotypic variability in CAKUT patients.

Conclusions

Congenital anomalies of kidneys and urinary tract reoccur in 10% of patients within the family. Mutations in different renal developmental genes seem to contribute to this recurrence. For each single gene involved the mutation detection rate seems low - with the exception of mutations in HNF1B which are causative for cystic dysplasia of the kidney. Modifier effects and oligogenic inheritance seem to be important for the pathogenesis of CAKUT complicating genetic counseling for affected families. In contrast, in patients with defined autosomal dominant disease, genetic counseling is of high clinical relevance, also with respect to additional extrarenal symptoms. It can be expected, that a large number of new CAKUT genes will be identified in the near future by using novel sequencing and bioinformatic technologies.

Key points

- Congenital anomalies of kidney and urinary tract (CAKUT) are identified with rising frequency due to the elevated frequency of routinely performed ultrasound examinations in the pre- and postnatal period.
- In approximatively 10% of cases other family members are also affected by CAKUT, suggesting a genetic component in the pathogenesis.
- Numerous genes have been identified in the last decade that is critically involved in early kidney development.
- For some of them an implication in human genetic disorders of kidney and urinary tract development have been reported.
- Genetic counseling is important in families with hereditary CAKUT, however, counseling can be difficult in cases with oligogenic inheritance.

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Sažetak

NOVI GENETSKI ASPEKTI KONGENITALNIH ANOMALIJA BUBREGA I MOKRAĆNOG SUSTAVA

S. WEBER

Svrha prikaza. Kongenitalne anomalije bubrega i mokraćnog sustava (CAKUT) spadaju u najčešće organske malformacije. One su značajan uzrok kroničnog bubrežnog zatajenja u djece. Osim izoliranih oblika CAKUT-a, u više od 500 sindroma anomalije mokraćnog sustava su kombinirane s anomalijama drugih organskih sustava. Obiteljska pojava bubrežnih malformacija u oko 10% bolesnika upućuje na njihovo moguće gensko podrijetlo. Modificirajući učinci zbog missense mutacija u dodatnim razvojnim genima vjerojatno omogućuju fenotipsku varijabilnost u zahvaćenim obiteljima. U tim obiteljima gensko savjetovanje može biti otežano. Za razliku od njih, u bolesnika s jasno određenom autosomno dominantnom bolešću, gensko savjetovanje je od velike kliničke važnosti, uzimajući u obzir i dodatne ekstrarenalne simptome.

Najnovije spoznaje: Zbog (1) razvijanja brojnih genskih knock-out modela miševa, (2) identifikacije specifičnih razvojnih gena bubrega i (3) primjene novih tehnika sekvencioniranja humanog genoma naše razumijevanje organogeneze bubrega se značajno poboljšalo tijekom zadnjih godina.

Sažetak: Ovaj pregled će se usredotočiti na važne genske čimbenike koji utječu na nefrogenezu i koji rasvjetljuju važne ljudske bolesti koje su povezane s bubrežnim anomalijama te proksimalnim i distalnim mokraćnim sustavom.