Ulusal Çocuk
9 Nefroloji Kongresi
24-27 Kasım 2016
Calista Luxury Resort
Antalya

CAKUT
(Tanım, kapsam ve patogenetik faktörler)

Mukaddes Kalyoncu
Karadeniz Teknik Üniversitesi Tıp Fakültesi
Çocuk Nefrolojisi TRABZON

Sunum Planı

- CAKUT'un
  - Tanımı
  - Kapsamı
- CAKUT gelişiminde rol alan patogenetik etmenler

Embriyoloji

- Üç evre
  - Pronefroz
    - 4. hf
  - Mezonefroz
    - 26. gün→ 5. hf
  - Metanefroz
    - >5. hf
    - 6-10. hf işlev

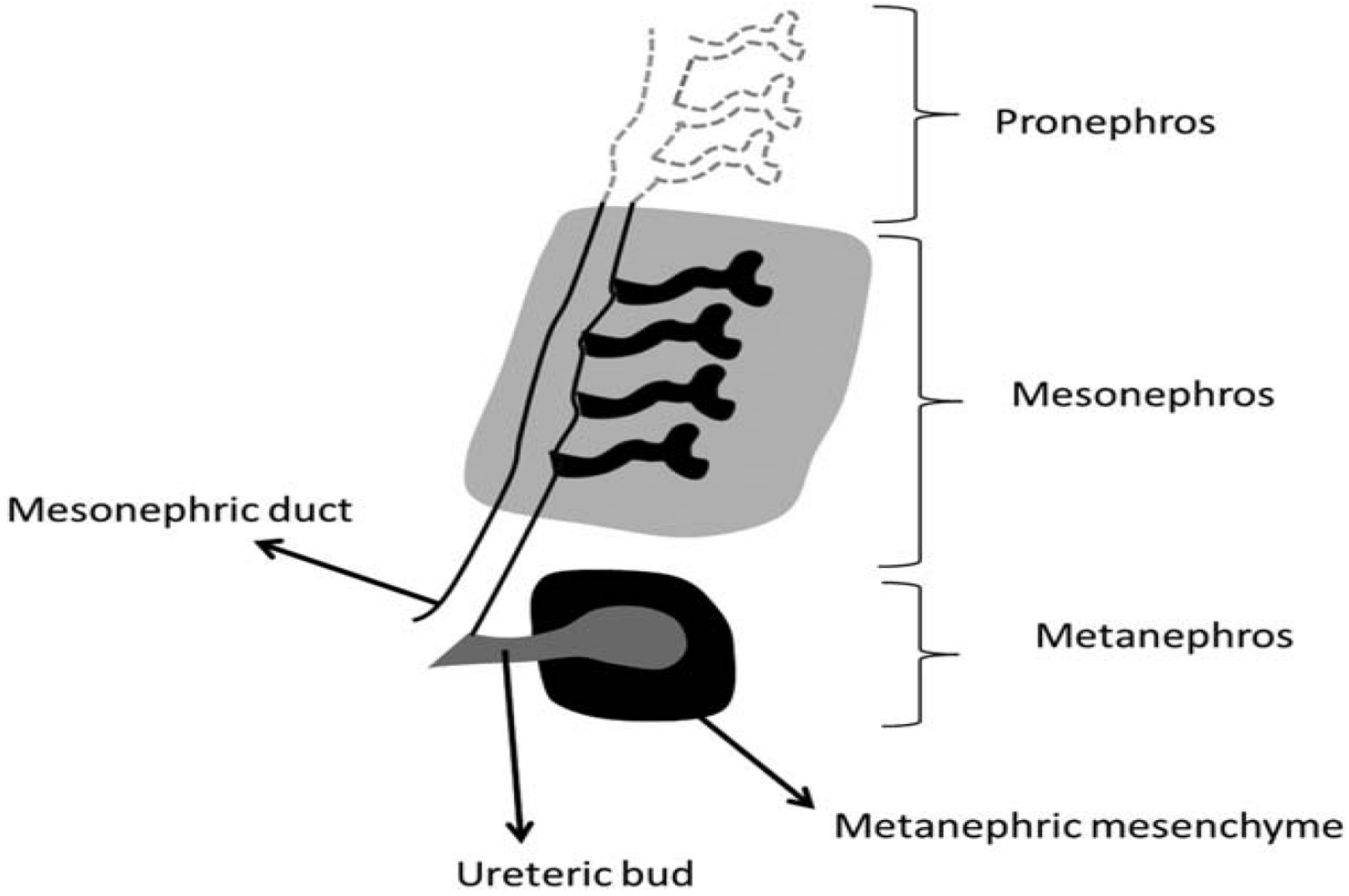


FIGURE 1. *Shows the early organogenesis of the kidney and urinary tract (Ichikawa et al., 2002).*

Embriyoloji

12- The development of the urinary tract (2).mp4

Tanım

Böbrek ve idrar yollarının

doğuştan anomalileri

Kapsam

- Üç grup
  - Böbrek parankim bozuklukları
  - Kusurlu göç
  - Toplayıcı sistem anomalileri

Böbrek parankim bozuklukları

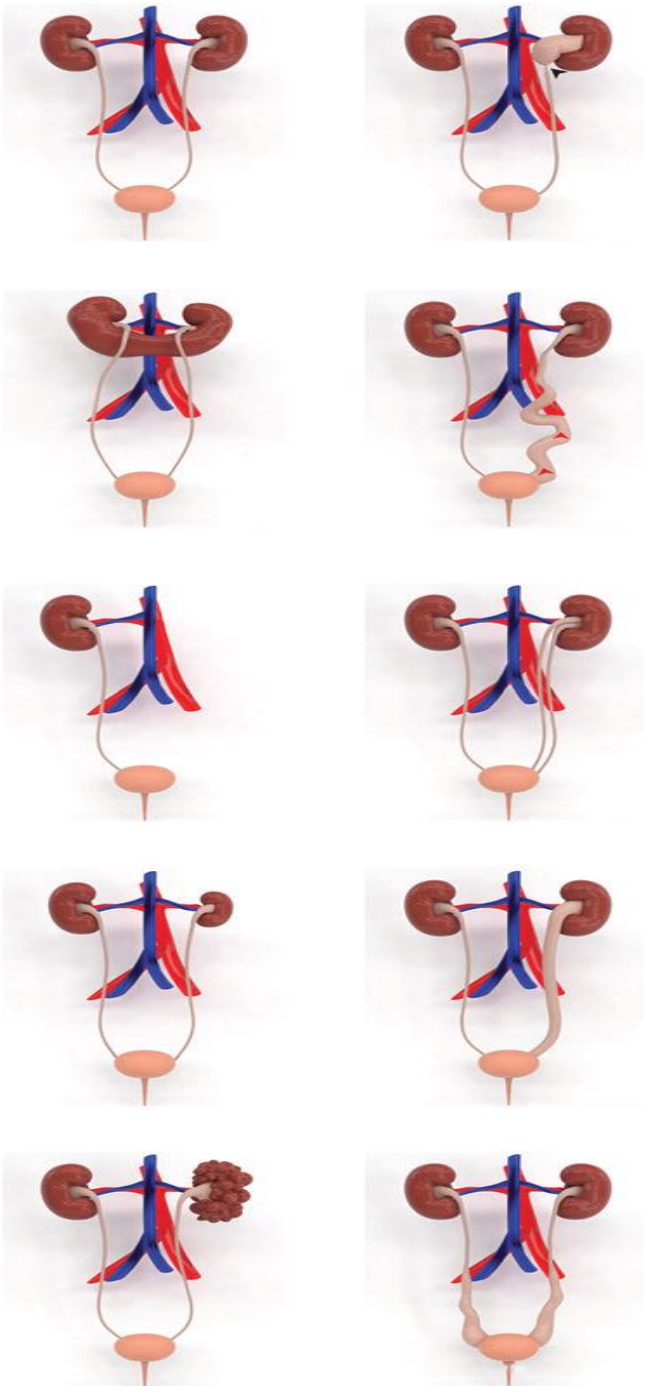
- Böbrek yokluğu
- Renal/tübüler displazi
- Böbreğin kistik hastalıkları…

Kusurlu göç

- Ektopik böbrek
  - Pelvik
- Füzyon anomalileri
  - Atnalı böbrek
- Karma
  - Krosektopik füzyone böbrek…

Toplayıcı sistem anomalileri

- Darlık
  - UVD, UPD, PÜV
- Vezikoüreteral reflü
- Çift toplayıcı sistem
- Mega/ektopik üreter
- Ekstrofiya vezikalis…



Neden önemli?

Son dönem böbrek

yetmezliği nedeni

(%35-50)

Patogenetik etmenler

- Çevresel etmenler
- Beslenme
- Tek gen
- miRNA

Genetic, environmental, and epigenetic factors involved in CAKUT

Nayia Nicolaou, Kirsten Y. Renkema, Ernie M. H. F. Bongers, Rachel H. Giles and Nine V. A. M. Knoers

Abstract | Congenital anomalies of the kidney and urinary tract (CAKUT) refer to a spectrum of structural renal malformations and are the leading cause of end-stage renal disease in children. The genetic diagnosis of CAKUT has proven to be challenging due to genetic and phenotypic heterogeneity and incomplete genetic penetrance. Monogenic causes of CAKUT have been identified using different approaches, including single gene screening, and gene panel and whole exome sequencing. The majority of the identified mutations, however, lack substantial evidence to support a pathogenic role in CAKUT. Copy number variants or single nucleotide variants that are associated with CAKUT have also been identified. Numerous studies support the influence of epigenetic and environmental factors on kidney development and the natural history of CAKUT, suggesting that the pathogenesis of this syndrome is multifactorial. In this Review we describe the current knowledge regarding the genetic susceptibility underlying CAKUT and the approaches used to investigate the genetic basis of CAKUT. We outline the associated environmental risk factors and epigenetic influences on CAKUT and discuss the challenges and strategies used to fully address the involvement and interplay of these factors in the pathogenesis of the disease.

Nicolaou, N. *et al. Nat. Rev. Nephrol.* advance online publication 18 August 2015; doi:10.1038/nrneph.2015.140

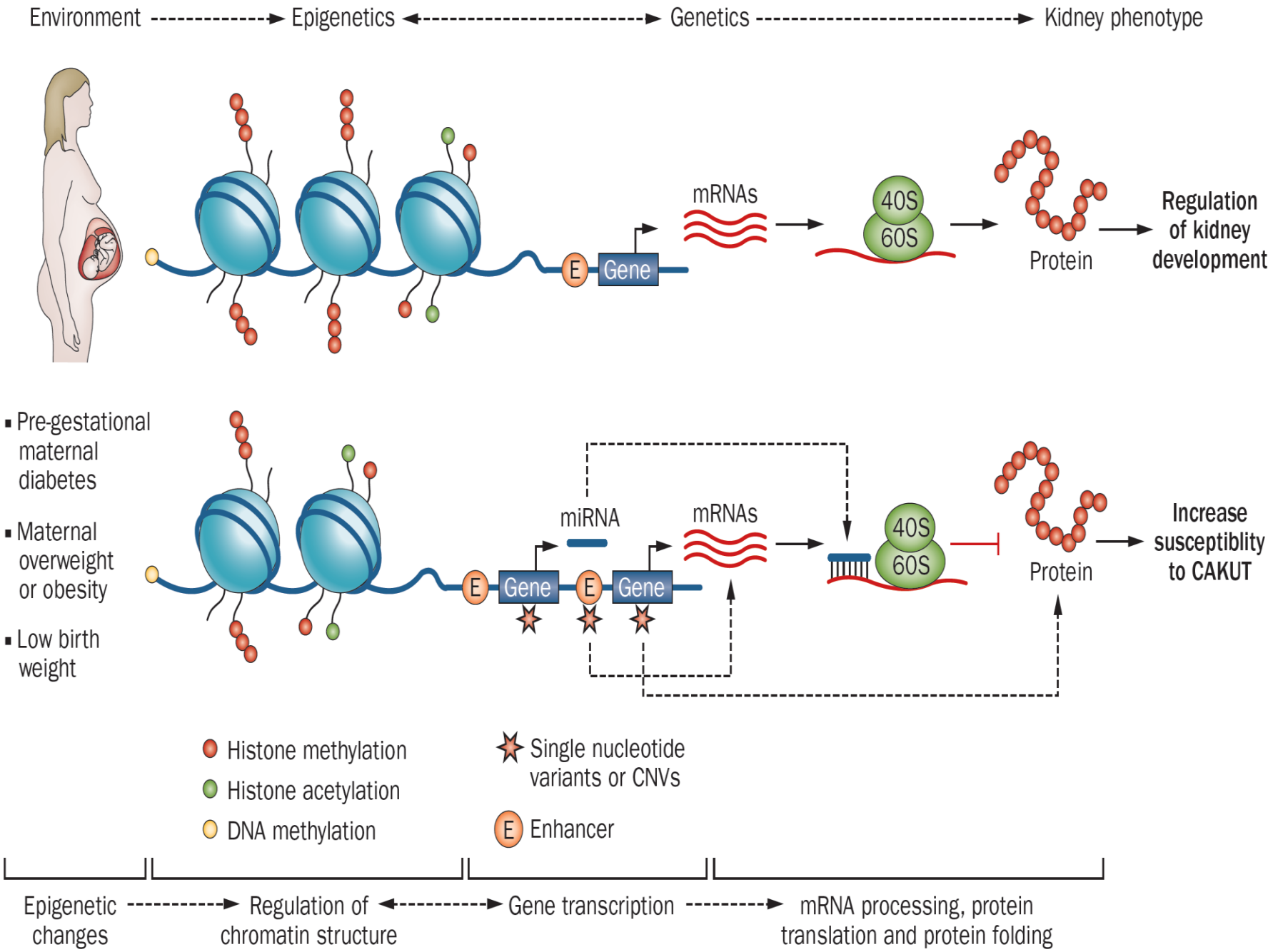


Figure 2 | The potential effect of the interplay between environmental, epigenetic, and genetic factors on kidney

Pediatrics International (2003) **45**, 610–616

Feature Article

Genetic disorders of human congenital anomalies of the kidney and urinary tract (CAKUT)

KOICHI NAKANISHI AND NORISHIGE YOSHIKAWA

Department of Pediatrics, Wakayama Medical University, Wakayama, Japan

Abstract Congenital abnormalities of the kidney and urinary tract, CAKUT are common in humans, occurring at a frequency of approximately 1 in 500 fetal ultrasound examinations. CAKUT are major causes of chronic renal failure in infants and young children, but little is known about the molecular pathogenesis of these disorders. To date, several gene mutations have been identified as a cause of human CAKUT: these include *PAX2*, *KAL*, *EYA1*, *AGTR2* and *HNF-1β*. At present, there is only limited information regarding how mutations alter gene expression during development to cause some CAKUT. The most convincing information comes from the multiorgan malformation syndromes with specific gene mutations. However, these syndromes are relatively rare, and most CAKUT appear to occur in isolation. The goal of this review is to provide an overview of these genetic disorders for CAKUT. An understanding of the genetic aspects of human CAKUT will help to unravel the pathogenesis of these disorders and may facilitate the design of genetic screening tests for early diagnosis and appropriate genetic counseling. Moreover, a deeper insight into the relationship between abnormal genes and the pathogenesis of abnormalities of CAKUT will provide an etiological classification of CAKUT. In addition, the importance of developing a registry of patients with various forms of CAKUT is discussed. This information will allow us to combine molecular biology and classical epidemiologic methods, and to continue expanding our knowledge regarding CAKUT.

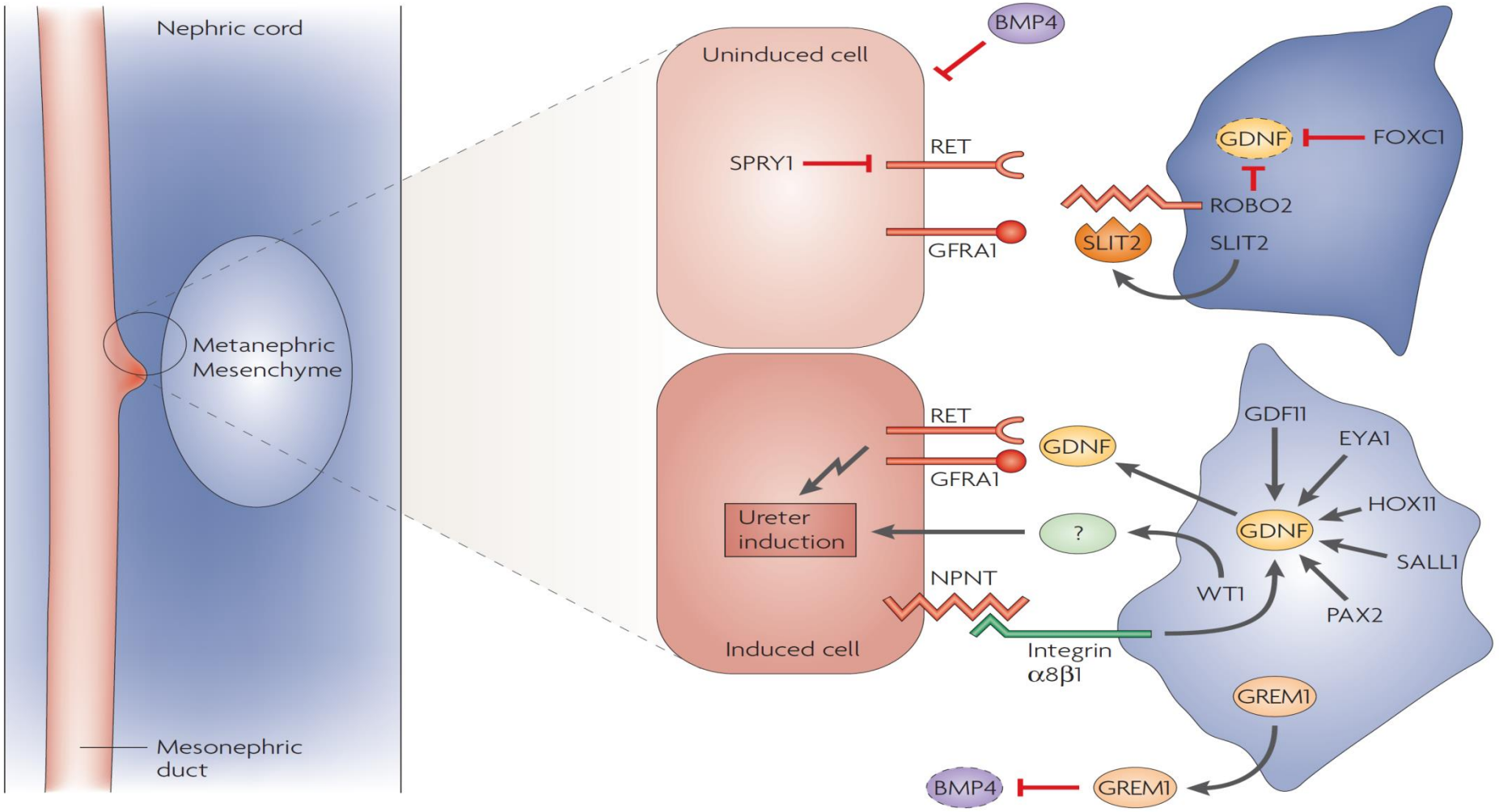


Figure 3 | **Molecular pathways that control kidney induction.** Mesenchymal cells at the caudal end of the nephrogenic cord (coloured light blue) express various factors that activate expression of glial-derived neurotrophic factor (GDNF). In addition, mesenchymal cells release gremlin 1 (GREM1), an inhibitor of bone morphogenetic protein (BMP) signalling, and other still unidentified factors. Released GDNF binds to RET and GDNF-family receptor α1 (GFRA1) receptors that are presented by epithelial cells of the mesonephric duct (coloured red) The combination of these signals induces ureteric budding. Mesenchymal cells at a more rostral level (coloured dark blue) express forkhead box protein C1 (FOXC1), Slit homologue 2 (SLIT2) and its receptor Roundabout homologue 2 (ROBO2), leading to a repression of GDNF. In epithelial cells of the mesonephric duct, the tyrosine kinase inhibitor sprouty 1 (Spry1) suppresses RET activation. Finally, BMP4 also inhibits ureter outgrowth. EYA1, Eyes-absent homologue 1; GDF11, growth differentiation factor 11; HOX11, homeobox protein 11; NPNT, nephronectin; WT1, Wilms tumour transcription factor.

REVIEW

2012

CURRENT OPINION

Novel genetic aspects of congenital anomalies of kidney and urinary tract

Stefanie Weber

Purpose of 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. Apart from 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 approximately 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 the development of numerous genetic knock-out mouse models, the identification of specific renal developmental genes and the application of novel sequencing techniques of the human genome, our understanding of kidney organogenesis has largely improved during very recent years.

Summary

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

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; Renal Cyst and Diabetes Syndrome (RCAD), maturity onset diabetes of the young (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)

ad, autosomal dominant; ar, autosomal recessive.

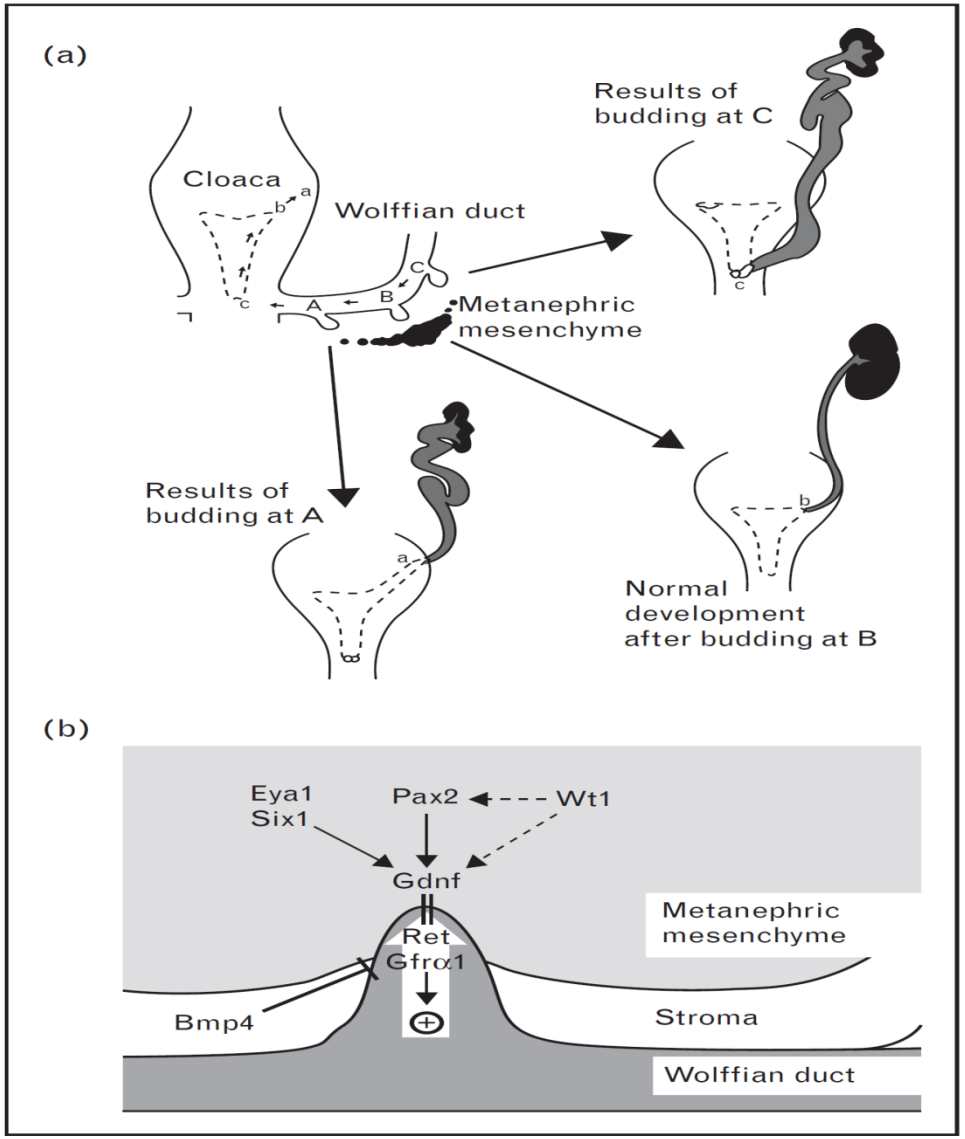


FIGURE 1. (a) The budding hypothesis: ectopic budding of the ureter (A, C) causes ectopia of the ureteral opening into the bladder (a, c) with consequent reflux or obstruction and dysplasia of the renal tissue (modified from [4]). (b) Budding of the ureter into the metanephric mesenchyme during early kidney development (provided by Raphael Schild, University Children's Hospital Hamburg, Germany).

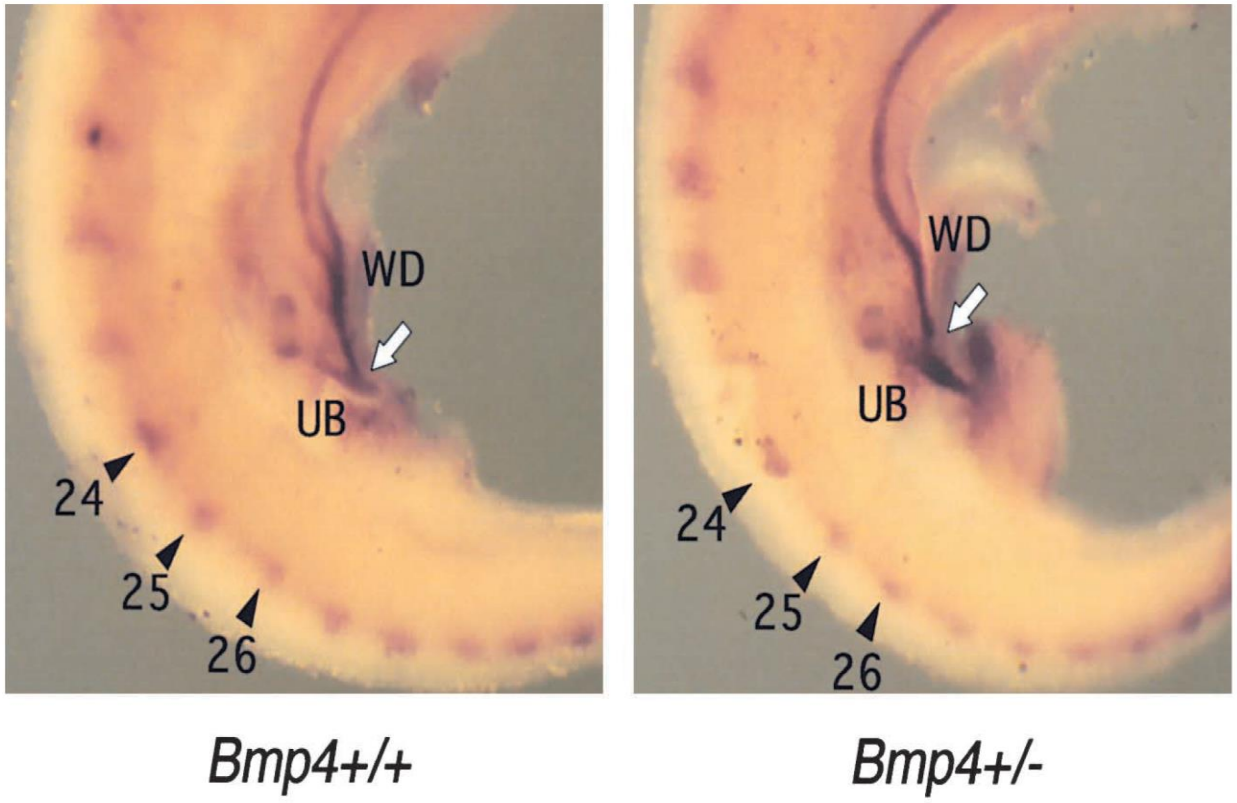


Fig. 3. Ectopic budding in a *Bmp4* mutant embryo. *c-ret* and *Wnt 11* whole mount in situ hybridization for wild-type and *Bmp4* +/− mutants at E11.0. The position of the initial ureter budding from the Wolffian duct is indicated by arrows, and the 24th, 25th and 26th somite pairs are marked by arrowheads. The position of the initial budding in the wild type corresponds to the ~26th somite, whereas that in the mutant corresponds to the ~25th somite. (WD) Wolffian duct; (UB) ureteric bud.

Renal abnormalities and their developmental origin

Andreas Schedl *‡

Abstract | Congenital abnormalities of the kidney and urinary tract (CAKUT) occur in 1 out of 500 newborns, and constitute approximately 20–30% of all anomalies identified in the prenatal period. CAKUT has a major role in renal failure, and there is increasing evidence that certain abnormalities predispose to the development of hypertension and cardiovascular disease in adult life. Moreover, defects in nephron formation can predispose to Wilms tumour, the most frequent solid tumour in children. To understand the basis of human renal diseases, it is essential to consider how the kidney develops.

The metanephros, or permanent kidney, is the main filtrating organ of the mammalian organism. Development of the kidney requires complex interactions between tissues that undergo various morphogenetic events. The basic structural and functional unit of the kidney is the nephron, which performs a multitude of tasks including blood filtration, re-absorption of salt, water and other compounds required by the body, and regulation of blood pressure and pH. These functions can be related to specific 'units' in each nephron that are formed in a recent insights into the molecular mechanisms that lead to nephron patterning along the proximal–distal axis.

Although it is easy to correlate developmental defects with particular stages of development, it is much more difficult to relate these findings to specific genes. This is mainly due to the fact that many genes fulfil various tasks during development, depending on their developmental context, a point that I will illustrate using examples of transcriptional regulators in kidney development.

Table1 | **Congenital abnormalities and genes that have been identified in human patients**

Renal congenital defects	Symptoms	Syndromes	Gene defects
Duplex (multiple) ureter	Formation of several ureters resulting from defective ureter induction	Usually no symptoms; can however be associated with hydroureter (see below)	
Hydronephrosis	Distention of the pelvis and calices of the kidney. Often the result of ureter obstruction	Ochoa (urofacial) syndrome	On Chr 10q23–q24
Megaureter	Increased ureter size; often coupled with VUR	Ellis van Crefeld (also renal agenesis)	*EVC*, *EVC2*
Nephrotic syndrome (NS)	Proteinuria resulting from a failure of blood filtration; usually caused by glomerular defects	Frasier, Denys–Drash, WAGR, idiopathic NS	*WT1*
		Finnish type NS	*NPHS1*
		Nail–patella–syndrome	*LMX1B*
		Pierson syndrome	*LAMB2*
		Steroid-resistant NS	*NPHS2*
Oligomeganephronia	Few large nephrons	Oligomeganephronia	*PAX2*
Polycystic kidneys	Formation of cysts affecting either tubules, collecting ducts or both	Renal cysts and diabetes	*HNF1B*
		Polycystic kidney disease (PKD)	*PKD1*, *PKD2*
		Polycystic kidney and hepatic disease (PKHD)	*PKHD1*
Renal aplasia (agenesis)	Absence of kidney; usually unilateral, but can occur bilaterally	Branchootorenal syndrome(BOR)	*EYA1*, *SIX1*, *SIX4*, *SIX5*
Renal hypoplasia	Reduction of kidney size without abnormal development, probably caused by a reduced number of nephrons	Renal-coloboma (also VUR)	*PAX2*
		Townes–Brocks	*SALL1*
		Pallister–Hall	*GLI3*
Renal dysplasia	Kidneys contain abnormally developed structures; often associated with hypoplasia (renal hypodysplasia)	Fraser (also hypoplasia or aplasia)	*FRAS1*, *FREM1*
		Campomelic dysplasia (also multicystic)	*SOX9*
		Senior–Loken syndrome (also multicystic)	*NPHP1*, *NPHP4*, *NPHP5*
Tubular dysgenesis	Defective proximal tubules formation	Renal tubular dysgenesis	*REN*, *AGT*, *ACE*, *AGTR1*
VUR	Movement of urine from the bladder to the ureter or kidney	VUR, VUR2	*GFRA1*←*ROBO2*

ACE, angiotensin I converting enzyme; *AGT*, angiotensinogen; *AGTR1*, angiotensin II receptor, type 1; Chr, chromosome; *EVC*, Ellis van Creveld gene; *EYA1*, Eyes-absent homologue 1; *FREM1*, FRAS1-related extracellular matrix protein 1 gene; *GFRA1*, GDNF family receptor α1; GLI3, GLI-Kruppel family member GLI3; *HNF1B*, hepatocyte nuclear factor 1β, also known as *TCF2* or *vHNF*; *LAMB2*, laminin, β2 (laminin S) gene; *LMX1B*, LIM homeobox transcription factor 1β gene; *NPHP*, nephronophthisis gene; *NPHS1*, nephrosis 1, congenital, Finnish type; *NPHS2*, nephrosis 2, idiopathic, steroid-resistant (podocin); PAX, paired-box gene; *REN*, renin; *ROBO2*, roundabout homologue 2; *SALL1*, Sal-like gene 1, SIX, sine oculis homeobox homologue; *SOX9*, SRY (sex determining region Y)-box 9; VUR, vesicoureteral reflux; WAGR, Wilms tumour–aniridia–genitourinary anomalies–mental retardation; WT1, Wilms tumour gene.

Congenital Anomalies of the Kidney and Urinary Tract: An Embryogenetic Review

Augusto Cesar Soares dos Santos Junior[1], Debora Marques de Miranda[1,2], and Ana Cristina Simões e Silva*[1,2]

Congenital anomalies of the kidney and urinary tract (CAKUT) represent a broad range of disorders that result from abnormalities of the urinary collecting system, abnormal embryonic migration of the kidneys, or abnormal renal parenchyma development. These disorders are commonly found in humans, accounting for 20–30% of all genetic malformations diagnosed during the prenatal period. It has been estimated that CAKUT are responsible for 30–50% of all children with chronic renal disease worldwide and that some anomalies can predispose to adult-onset diseases, such as hypertension. Currently, there is much speculation regarding the pathogenesis of CAKUT. Common genetic background with variable penetrance plays a role in the development of the wide spectrum of CAKUT phenotypes. This review aims to summarize the possible mechanisms by which genes responsible for kidney and urinary tract morphogenesis might be implicated in the pathogenesis of CAKUT.

Birth Defects Research (Part C) 102:374–381, 2014.
© 2014 Wiley Periodicals, Inc.

Key words: CAKUT; polymorphisms; morphogenesis; chronic kidney disease

TABLE 1. *Main Single-Gene Mutations Associated with Nonsyndromic Human CAKUT*

Gene	Phenotype	References
AGTR2	Ureteropelvic junction obstruction, megaureter, multicystic dysplastic kidney, hydronephrosis, posterior urethral valves	(Nishimura et al., 1999; Oshima et al., 2001; Nakanishi and Yoshikawa, 2003; Hahn et al., 2005; Miranda et al., 2014)
BMP4	Renal hypodysplasia	(Miyazaki et al., 2000; Hoshino et al., 2008; Weber et al., 2008a; Chi et al., 2011; Paces-Fessy et al., 2012; Dos Reis et al., 2014)
EYA1	Branchio-oto-renal (BOR) syndrome	(Abdelhak et al., 1997)
PAX2	Hipoplasia renal, coloboma renal, Vesicoureteral reflux	(Dressler et al., 1993; Nakanishi and Yoshikawa, 2003; Dziarmaga et al., 2006; Chen et al., 2008; Harshman and Brophy, 2012; de Miranda et al., 2014)
SALL	Townes-Brocks Syndrome	(Nishinakamura et al., 2001; Nishinakamura and Takasato, 2005)
SIX1	Branchio-oto-renal (BOR) syndrome	(Ruf et al., 2004)
SIX5	Branchio-oto-renal (BOR) syndrome	(Hoskins et al., 2007)

Fetal and Pediatric Pathology, 33:293–320, 2014
Copyright © Informa Healthcare USA, Inc
ISSN: 1551-3815 print / 1551-3823 online
DOI: 10.3109/15513815.2014.959678

informa
healthcare

ORIGINAL ARTICLE

Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT)

Maria M. Rodriguez

Holtz Children's Hospital Department of Pathology, Pediatric Pathology, University of Miami, Coral Gables, FL, USA

This article reviews the majority of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) with emphasis in Pediatric Pathology describing and illustrating lesions as varied as ureteral duplications, ureteropelvic junction obstruction, horseshoe kidney, posterior urethral valve and prune belly syndrome, obstructive renal dysplasia, nonmotile ciliopathies and several syndromes associated with renal malformations (Meckel–Joubert, short rib, Bardet–Biedl, asplenia/polysplenia, hereditary renal adysplasia, Zellweger, trisomies, VACTER-L, Potter, caudal dysplasia, and sirenomelia), as well as ADPK, and ARPK.

The purpose of this review is not only to describe the congenital renal anomalies, but also to analyze the more recent therapeutic interventions that may modify the natural history of some of these severe conditions.

Kidney International, Vol. 54, Suppl. 67 (1998), pp. S-75–S-77

HYPERTENSION, VASCULAR DISEASE

Role of angiotensin in the congenital anomalies of the kidney and urinary tract in the mouse and the human

ELIZABETH YERKES, HIDEKI NISHIMURA, YOUICHI MIYAZAKI, SHINYA TSUCHIDA, JOHN W. BROCK III, and IEKUNI ICHIKAWA

Departments of Pediatrics, Medicine and Urology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Role of angiotensin in kidney and urinary tract congenital anomalies in the mouse and the human. The role of angiotensin in fluid and electrolyte and blood pressure homeostasis is well known. Recent developments indicate that angiotensin has a profound role not only in the developing urinary tract but also in the response of the urinary tract to specific noxious stimuli. Furthermore, the role of angiotensin II and its receptor has been understood quite poorly with respect to the developing renal unit. Knockout mice for the ATR2 gene show a significant incidence of congenital urinary tract anomalies. The congenital anomalies of the kidney and urinary tract (CAKUT) seen in these mice are very similar to the anomalies observed in humans. This has been supported further by the finding of an abnormality in the genetic sequence in patients with CAKUT. This article reviews experimental laboratory data as well as the potential implications for humans.

environment, and Ang is a biological tool to perform this function.

Renin-angiotensin release also surges when urine outflow is mechanically hindered (Fig. 1) [4]. This phenomenon of ureteral pressure-sensitive activation of renin-angiotensin has been heretofore viewed as an error of nature and often even as harmful to the kidney [5]. The challenge to this traditional view came when we examined several strains of mutant mice that are completely devoid of either Ang type 1 (AT1) receptor gene (*Agtr1*) or Ang type 2 (AT2) receptor gene (*Agtr2*) as a result of genetic manipulation of these genes [6, 7]. As discussed in more detail later here, these strains of mice display varying degrees of urinary tract obstruction, either structural or functional in nature. Some obstructions develop during early kidney

NIH Public Access
Author Manuscript
Keio J Med. Author manuscript; available in PMC 2009 July 28.

Published in final edited form as:
Keio J Med. 2008 December ; 57(4): 184–189.

A New Role for the Renin-Angiotensin System in the Development of the Ureteric Bud and Renal Collecting System

Ihor V. Yosypiv, M.D.
Division of Pediatric Nephrology, Department of Pediatrics, Tulane University Health Sciences Center, New Orleans, LA 70112

Abstract

The renin-angiotensin system (RAS) plays a critical role in kidney development. Mutations in the genes encoding components of the RAS or pharmacological inhibition of RAS in mice or humans cause a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT). The observed defects include renal vascular abnormalities, abnormal glomerulogenesis, renal papillary hypoplasia, hydronephrosis, aberrant ureteric bud (UB) budding, duplicated collecting system and renal tubular dysgenesis. Little is known about the potential role of Ang II and its receptors in the morphogenesis of the UB and renal collecting system. This review emphasizes a novel role for the RAS in the development of the ureteric bud, collecting ducts and renal medulla. We observe that UB and surrounding stroma express angiotensinogen and Ang II AT_1 receptors (AT_1R) *in vivo*. Ang II stimulates UB cell branching in collagen gel cultures *in vitro* and induces UB morphogenesis in intact whole embryonic metanephroi grown *ex vivo*. In contrast, treatment of metanephroi with the AT_1R antagonist candesartan inhibits UB branching. In addition, Ang II induces tyrosine phosphorylation of the epidermal growth factor receptor (EGFR) in UB cells. Furthermore, Ang II-stimulated UB morphogenesis is abrogated by inhibition of EGFR tyrosine kinase activity. In summary: 1) Ang II, acting *via* the AT_1R, stimulates UB branching; 2) This process depends on tyrosine phosphorylation of the EGFR. Together, these data indicate that cooperation of AT_1R and EGFR signaling performs essential functions during renal collecting system development *via* control of UB branching morphogenesis.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Pediatr Nephrol (2011) 26:1499–1512
DOI 10.1007/s00467-011-1820-2

REVIEW

Renin–angiotensin system in ureteric bud branching morphogenesis: insights into the mechanisms

Ihor V. Yosypiv

Received: 9 November 2010 / Revised: 24 January 2011 / Accepted: 1 February 2011 / Published online: 26 February 2011
© IPNA 2011

Abstract Branching morphogenesis of the ureteric bud (UB) is a key developmental process that controls organogenesis of the entire metanephros. Notably, aberrant UB branching may result in a spectrum of congenital anomalies of the kidney and urinary tract (CAKUT). Genetic, biochemical and physiological studies have demonstrated that the renin–angiotensin system (RAS), a key regulator of the blood pressure and fluid/electrolyte homeostasis, also plays a critical role in kidney development. All the components of the RAS are expressed in the metanephros. Moreover, mutations in the genes encoding components of the RAS in mice or humans cause diverse types of CAKUT which include renal papillary hypoplasia, hydronephrosis, duplicated collecting system, renal tubular dysgenesis, renal vascular abnormalities, abnormal glomerulogenesis and urinary concentrating defect. Despite widely accepted role of the RAS in metanephric kidney and renal collecting system (ureter, pelvis, calyces and collecting ducts) development, the mechanisms by which an intact RAS exerts its morphogenetic actions are incompletely defined. Emerging evidence indicates that defects in UB branching morphogenesis may be causally linked to the pathogenesis of renal collecting system anomalies observed under conditions of aberrant RAS signaling. This review describes the role of the RAS in UB branching morphogenesis and highlights emerging insights into the cellular and molecular mechanisms whereby RAS regulates this critical morphogenetic process.

Keywords Kidney development · Ureteric bud · Renin-angiotensin · GDNF · Ret · EGF receptor

Introduction

Branching morphogenesis of the ureteric bud (UB) is a fundamental developmental process that controls organogenesis of the metanephros. Notably, derangements in UB morphogenesis cause a spectrum of congenital anomalies of the kidney and urinary tract (CAKUT), the major cause of renal failure in children [1]. Recent advances broadened our knowledge on the genetic and molecular mechanisms that orchestrate UB morphogenesis and provided new insights into the pathogenesis of CAKUT [2, 3]. The critical role of the renin–angiotensin system (RAS) in kidney and urinary tract morphogenesis is evident from occurrence of diverse forms of CAKUT in animals or humans as a result of RAS gene mutations. These forms of CAKUT include papillary and medullary hypodysplasia, hydronephrosis, renal tubular dysgenesis, duplicated collecting system and urinary concentrating defect (Table 1) [4–11].

Pediatr Nephrol (2014) 29:609–620
DOI 10.1007/s00467-013-2616-3

REVIEW

Renin–angiotensin system in ureteric bud branching morphogenesis: implications for kidney disease

Ihor V. Yosypiv

Received: 18 June 2013 / Revised: 20 August 2013 / Accepted: 21 August 2013 / Published online: 7 September 2013
© IPNA 2013

Abstract Failure of normal branching morphogenesis of the ureteric bud (UB), a key ontogenic process that controls organogenesis of the metanephric kidney, leads to congenital anomalies of the kidney and urinary tract (CAKUT), the leading cause of end-stage kidney disease in children. Recent studies have revealed a central role of the renin–angiotensin system (RAS), the cardinal regulator of blood pressure and fluid/electrolyte homeostasis, in the control of normal kidney development. Mice or humans with mutations in the *RAS* genes exhibit a spectrum of CAKUT which includes renal medullary hypoplasia, hydronephrosis, renal hypodysplasia, duplicated renal collecting system and renal tubular dysgenesis. Emerging evidence indicates that severe hypoplasia of the inner medulla and papilla observed in *angiotensinogen* (*Agt*)- or angiotensin (Ang) II *AT$_1$ receptor* (*AT$_1$R*)-deficient mice is due to aberrant UB branching morphogenesis resulting from disrupted RAS signaling. Lack of the prorenin receptor (*PRR*) in the UB in mice causes reduced UB branching, resulting in decreased nephron endowment, marked kidney hypoplasia, urinary concentrating and acidification defects. This review provides a mechanistic rational supporting the hypothesis that aberrant signaling of the intrarenal RAS during distinct stages of metanephric kidney development contributes to the pathogenesis of the broad phenotypic spectrum of CAKUT. As aberrant RAS signaling impairs normal renal development, these findings advocate caution for the use of RAS inhibitors in early infancy and further underscore a need to avoid their use during pregnancy and to identify the types of molecular processes that can be targeted for clinical intervention.

Keywords Kidney development · Ureteric bud · Renin–angiotensin · Prorenin receptor · Cakut

Introduction

Metanephric kidney develops through reciprocal inductive interactions between the ureteric bud (UB) and the metanephric mesenchyme [1–3]. Induced by mesenchymal signals, the UB elongates and undergoes repetitive dichotomous branching to form the renal collecting system [collecting ducts (CDs), pelvis, and ureter] [1–3]. In turn, UB tips stimulate the mesenchyme to differentiate into nephron epithelia, progressing from renal vesicles, to comma-shaped bodies, to S-shaped bodies, to mature nephron consisting of the proximal tubule, the loop of Henle and the distal tubule [1–3]. These morphogenetic events are tightly controlled by multiple gene regulatory networks [1–3]. Abnormal UB branching results in a spectrum of congenital anomalies of the kidney and urinary tract (CAKUT), the major cause of end-stage kidney disease in children [4].

The renin–angiotensin system (RAS), the cardinal regulator of blood pressure and fluid/electrolyte homeostasis is also critical for normal kidney development [5–11]. Here I discuss molecular and cellular mechanisms by which an intact RAS directs UB branching, renal collecting system development and metanephric organogenesis. This review provides new insights into the pathogenesis of CAKUT that result from disrupted RAS signaling.

Effect of Drugs on Renal Development

Michiel F. Schreuder, Ruud R. Bueters,* Marleen C. Huigen,† Frans G.M. Russel,‡ Rosalinde Masereeuw,‡ and Lambertus P. van den Heuvel*†*

Summary

Many nephrotoxic effects of drugs have been described, whereas the effect on renal development has received less attention. Nephrogenesis ceases at approximately 36 weeks of gestation, indicating that drugs administered to pregnant women and to preterm-born neonates may influence kidney development. Such an effect on renal development may lead to a wide spectrum of renal malformations (congenital anomalies of the kidney and urinary tract [CAKUT]), ranging from renal agenesis to a reduced nephron number. Any of these anomalies may have long-term sequelae, and CAKUT is the primary cause for renal replacement therapy in childhood. This review focuses on research into the effect of drug treatment during active nephrogenesis during pregnancy and in preterm-born infants. Because the effects of many widely used drugs have not been unraveled thus far, more research is needed to study the effect on renal development and long-term renal sequelae after drug treatment during nephrogenesis.

Clin J Am Soc Nephrol 6: 212–217, 2011. doi: 10.2215/CJN.04740510

Table 1. Drugs shown to influence renal development

Drug	Effect of Maternal Treatment during Pregnancy on Offspring Kidney Development	Effect of Treatment during Postnatal Kidney Development
Aminoglycosides	Tubular alterations (16), low nephron number (17–19)	Tubular damage (21), low nephron number (19)
Cyclosporin A	Low nephron number (22)	
Prostaglandin synthetase inhibitors	Tubular alterations (21), similar nephron number (28)	Glomerular and tubular injury (21), similar nephron number (21,26,27)
ACEIs/ARBs	Renal insufficiency (31)	Atrophy of the renal papilla, tubular alterations (32), low nephron number (33)
Dexamethasone	Altered tubular transporters (36,37), low nephron number (5), similar nephron number (38)	Low nephron number (5,35)
Furosemide	Renal concentrating defect (40)	—
Antiepileptic drugs	More congenital malformations, specifically MCDK (44)	—
Mycophenolate mofetil	Renal agenesis/ectopia (45,46)	—
Adriamycin	Bladder agenesis, hydronephrosis (48)	—
Cyclophosphamide	Hydro(uretero)nephrosis (49)	—

MCDK, multicystic dysplastic kidney.

Pediatr Nephrol (2011) 26:353–364
DOI 10.1007/s00467-010-1529-4

REVIEW

Genetics of congenital anomalies of the kidney and urinary tract

Renfang Song · Ihor V. Yosypiv

Received: 29 March 2010 / Revised: 8 July 2010 / Accepted: 13 July 2010 / Published online: 27 August 2010
© IPNA 2010

Abstract Congenital anomalies of the kidney and urinary tract (CAKUT) occur in 1 in 500 births and are a major cause of morbidity in children. Notably, CAKUT account for the most cases of pediatric end-stage renal disease and predispose the individual to hypertension and cardiovascular disease throughout life. Although some forms of CAKUT are a part of a syndrome or are associated with a positive family history, most cases of renal system anomalies are sporadic and isolated to the urinary tract. Broad phenotypic spectrum of CAKUT and variability in genotype–phenotype correlation indicate that pathogenesis of CAKUT is a complex process that depends on interplay of many factors. This review focuses on the genetic mechanisms (single-gene mutations, modifier genes) leading to renal system anomalies in humans and discusses emerging insights into the role of epigenetics, in utero environmental factors, and micro-RNAs (miRNAs) in the pathogenesis of CAKUT. Common gene networks that function in defined temporospatial fashion to orchestrate renal system morphogenesis are highlighted. Derangements in cellular, molecular, and morphogenetic mechanisms that direct normal renal system development are emphasized as a major cause of CAKUT. Integrated understanding of how morphogenetic process disruptions are linked to CAKUT will enable improved diagnosis, treatment, and prevention of congenital renal system anomalies and their consequences.

Keywords Kidney development · CAKUT · Renal hypodysplasia · Renin-angiotensin

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) occur at a frequency of 1 in 500 live births [1, 2]. CAKUT comprise a spectrum of renal tract malformations that occur at the level of the kidney (e.g. hypoplasia, dysplasia), collecting system (e.g. hydronephrosis, megaureter), bladder (e.g. ureterocele, vesicoureteral reflux), or urethra (e.g. posterior urethral valves) (Table 1). Although some forms of CAKUT are a part of a syndrome or are

Kidney International, Vol. 61 (2002), pp. 889–898

PERSPECTIVES IN RENAL MEDICINE

Paradigm shift from classic anatomic theories to contemporary cell biological views of CAKUT

Iekuni Ichikawa, Fumiyo Kuwayama, John C. Pope IV, F. Douglas Stephens, and Yoichi Miyazaki

Departments of Pediatrics, Medicine and Urologic Surgery, Vanderbilt University Medical Center Nashville, Tennessee, USA; Department of Pediatrics, Tokai University School of Medicine, Isehara, Japan; Department of Surgery, Royal Children's Hospital, Melbourne, Australia; and Department of Medicine, Jikei University School of Medicine, Tokyo, Japan

Paradigm shift from classic antatomic theories to contemporary cell biological views of CAKUT. Ectopic budding of the ureter from the Wolffian duct is the first ontogenic misstep that leads to many—if not all—congenital anomalies of the kidney and urinary tract (CAKUT). The ectopia results in hypoplastic kidney, ectopia of ureterovesical orifice, urinary outflow obstruction and/or reflux. Studies in several mutant mouse models have verified that ectopic ureteric budding indeed precedes formation of CAKUT. Often, the genes involved in navigating ureteric budding to the correct site also regulate later ontogenic events of the kidney and urinary tract. The wide spectrum of CAKUT, for example, multicystic dysplastic kidney, megaureter and atretic ureter, portray the additional important functions of these same genes that are activated at multiple sites and stages during the normal morphogenesis of the kidney and urinary tract

verse relationship, namely that the ureter promotes differentiation of the metanephric mesoderm.

Nephrologists often regard the ureter and below as merely a conduit, whereas urologists tend to regard the kidney as an extension of the urinary tract. As a result, the implicit inclusion of kidney anomalies in urologic studies [2] have failed to attain the deserved recognition of their achievement by the nephrology community.

The need emerged to coin the term, "CAKUT" (congenital anomalies of the kidney and urinary tract), which explicitly states the relevance to both urology [3] and nephrology communities [4].

Journal of Pediatric Urology (2006) 2, 2—9

Journal of Pediatric urology

REVIEW ARTICLE

Congenital anomalies of the kidney and urinary tract (CAKUT): A current review of cell signaling processes in ureteral development

D. Alan Stahl*, **Hari K. Koul**, **Job K. Chacko**, **Gerald C. Mingin**

Department of Surgery-Division of Urology, University of Colorado Health Science Center, 4200 East 9th Avenue, Campus Box C319, Denver, CO 80262, USA

Received 5 April 2005; accepted 29 April 2005
Available online 11 July 2005

KEYWORDS
Wolffian duct;
Ureteral development

Abstract *Objective:* The objective of this review is to present a concise summary of the genetic signaling processes involved in abnormal mouse Wolffian development and their correlation to those abnormalities affecting ureteral development in children.
Materials and methods: We performed an extensive review of the current literature pertaining to mouse Wolffian duct development and combined these findings with our own data.
Conclusion: This article reviews embryological findings in mice with ureteral abnormalities and draws connections between the mouse anomaly and what is seen in children. A review of the current literature has led to the identification of a number of genes which may prove to be important in understanding the causes of these anomalies.
© 2005 Journal of Pediatric Urology Company. Published by Elsevier Ltd. All rights reserved.

Pediatr Nephrol (2013) 28:689–698
DOI 10.1007/s00467-012-2223-8

REVIEW

Histone deacetylases in kidney development: implications for disease and therapy

Shaowei Chen · Samir S. El-Dahr

Received: 4 April 2012 / Revised: 15 May 2012 / Accepted: 17 May 2012 / Published online: 22 June 2012
© IPNA 2012

Abstract Histone deacetylases (HDACs) are an evolutionarily conserved group of enzymes that regulate a broad range of biological processes through removal of acetyl groups from histones as well as non-histone proteins. Recent studies using a variety of pharmacological inhibitors and genetic models of HDACs have revealed a central role of HDACs in control of kidney development. These findings provide new insights into the epigenetic mechanisms underlying congenital anomalies of the kidney and urinary tract (CAKUT) and implicate the potential of HDACs as therapeutic targets in kidney diseases, such as cystic kidney diseases and renal cell cancers. Determining the specific functions of individual HDAC members would be an important task of future research.

Keywords Histone deacetylases · Histone acetylation · Kidney development · CAKUT · Polycystic kidney disease

less than 4 years of age (North American Pediatric Renal Trials and Collaborative Studies 2008 Annual report). Notably, although some forms are familial and syndromic, most cases of CAKUT are sporadic and nonsyndromic. Given the complexity of CAKUT, to date, only a few genetic mutations have been identified for the syndromic forms of CAKUT, while the cellular and molecular basis of the more common nonsyndromic forms of CAKUT are largely unknown [1].

Thanks to the advances in molecular biology and gene targeting technology, recent years have witnessed an emerging awareness of the critical role of epigenetic mechanisms in health and disease. During embryogenesis, epigenetic modifications, such as DNA methylation, histone acetylation, histone phosphorylation and histone methylation, are set in the chromatin of developmental regulators; this in turn, determines the genome programming in a particular cell by modulating chromatin structure and thus DNA accessibility to the transcription-

J Am Soc Nephrol 10: 2018–2028, 1999

How They Begin and How They End: Classic and New Theories for the Development and Deterioration of Congenital Anomalies of the Kidney and Urinary Tract, CAKUT

JOHN C. POPE IV, JOHN W. BROCK III, MARK C. ADAMS, F. DOUGLAS STEPHENS, and IEKUNI ICHIKAWA
Vanderbilt University Medical Center, Nashville, Tennessee.

CAKUT, a Family of Diseases with a Diverse Anatomical Spectrum

Congenital anomalies of the kidney and urinary tract (CAKUT) account for more than 50% of abdominal masses found in neonates and involve some 0.5% of all pregnancies (1,2). Despite recent advancements in prenatal diagnosis and early surgical intervention, these anomalies still remain the primary cause of kidney failure in infants. Notably, the therapeutic interventions that are available to adults and older children, such as kidney transplantation, are often not feasible in infants.

Ureteropelvic junction (UPJ) obstruction (*e.g.*, stenosis or atresia) is the most common cause of a palpable abdominal mass in the newborn (3). Other forms of CAKUT include multicystic dysplastic kidneys (MCDK); hypoplastic kidneys (HK); vesicoureteral reflux (VUR); nonobstructed, nonrefluxing primary megaureter (MU); and bladder outlet obstruction (13). It is therefore believed that these *assorted anatomical anomalies* share a common genetic cause (14,15).

Genetic analyses on a number of families identified several different chromosomal loci that are associated with CAKUT. Indeed, a number of syndromes that involve multiple organ anomalies, including that of the kidney and urinary tract system, have been reported to take specific inheritance patterns, some autosomal dominant or recessive (16) and others X-linked dominant or recessive (17). Moreover, recent genetic analyses on several families identified several different chromosomal loci that are associated with CAKUT (18–20), although no specific gene involved has been identified from these studies. Most recently, the PAX2 gene was identified as the first specific gene whose mutation is associated with CAKUT (21). In view of the extremely high penetrance rate (autosomal dominant) of this anomaly within the same family

Pediatr Nephrol. 2014 April ; 29(4): 695–704. doi:10.1007/s00467-013-2684-4.

Single-Gene Causes of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in Humans

Asaf Vivante[1,2], **Stefan Kohl**[1], **Daw-Yang Hwang**[1], **Gabriel C. Dworschak**[1], and **Friedhelm Hildebrandt**[1,3]

[1]Department of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA

[2]Talpiot Medical Leadership Program, Sheba Medical Center, Tel-Hashomer, Israel

[3]Howard Hughes Medical Institute, Chevy Chase, MD, USA

Abstract

Congenital anomalies of the kidney and urinary tract (CAKUT) cover a wide range of structural malformations that result from defects in the morphogenesis of the kidney and/or urinary tract. These anomalies account for about 40–50% of children with chronic kidney disease worldwide. Knowledge from genetically modified mouse models suggests that single gene mutations in renal developmental genes may lead to CAKUT in humans. However, until recently only a handful of CAKUT-causing genes were reported, most of them in familial syndromic cases. Recent findings suggest that CAKUT may arise from mutations in a multitude of different single gene causes. We focus here on single gene causes of CAKUT and their developmental origin. Currently more than 20 monogenic CAKUT-causing genes have been identified. High-throughput sequencing techniques make it likely that additional CAKUT-causing genes will be identified in the near future.

Pediatr Nephrol (2012) 27:1265–1275
DOI 10.1007/s00467-011-2053-0

EDUCATIONAL REVIEW

PAX2 in human kidney malformations and disease

Lyndsay A. Harshman · Patrick D. Brophy

Received: 2 July 2011 / Revised: 10 October 2011 / Accepted: 18 October 2011 / Published online: 3 December 2011
© IPNA 2011

Abstract Human *PAX2* mutations have been associated with abnormalities in the developing and adult kidney ranging from congenital abnormalities of the kidney and urinary tract (CAKUT) to oncogenic processes. Defining the relationship of *PAX2* to human renal disease requires an appreciation of its fundamental role in renal development. Given the highly conserved nature of the *PAX2* gene in vertebrates, it is not surprising that much of our understanding of *PAX2* involvement in renal disease has been derived from animal models. The following review will outline the current evidence supporting involvement of *PAX2* in the pathologic processes involving the kidney.

Keywords *PAX2* · CAKUT · Epigenetics · Kidney malformations · Renal development · Oncogenesis

increased or decreased, across the lifespan is thought to be detrimental to renal function and structure.

Renal development and *PAX2*

PAX2 expression is necessary for formation of the metanephros within the developing intermediate mesoderm at approximately 4–5 weeks of gestation in humans and is required for the differentiation of mesenchymal cells to primitive, proliferating epithelium [1, 2]. During mesenchymal differentiation, expression of *PAX2* can be noted in the formation of several key renal structures, including the renal vesicles, comma-shaped bodies, S-shaped body, and later, the renal glomeruli and tubules (see Fig. 1) [3–5]. In

Seminars in Cell & Developmental Biology 44 (2015) 97–106

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Pax genes in renal development, disease and regeneration

Richa Sharma [1], Oraly Sanchez-Ferras [1], Maxime Bouchard *

Goodman Cancer Research Centre and Department of Biochemistry, McGill University, Montreal, Canada

ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form
15 September 2015
Accepted 21 September 2015
Available online 26 September 2015

Keywords:
Pax2
Pax8
Kidney and urinary tract development
CAKUT
Wilms' tumor
Renal cell carcinoma

ABSTRACT

The execution of developmental programs entails specific spatio-temporal expression of transcriptional regulators that ultimately control tissue morphogenesis and embryo patterning. Pax transcription factors are sequence-specific DNA-binding proteins exerting such regulatory activity in several tissues. In the urogenital system, Pax2 and Pax8 have emerged as crucial players at multiple steps of kidney and urinary tract development. They are involved in important processes such as cell survival, cell lineage decisions and tissue interactions through the regulation of sophisticated gene regulatory networks. Pax2/8 have additionally been directly associated with Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) and renal cancers in human. In this review, we provide an overview of landmark contributions to the understanding of *Pax* gene function in urinary tract development and disease with an emphasis on recent advances in the field.

© 2015 Elsevier Ltd. All rights reserved.

Review Article

Receptor Tyrosine Kinases in Kidney Development

Renfang Song, Samir S. El-Dahr, and Ihor V. Yosypiv

Section of Pediatric Nephrology, Department of Pediatrics, Hypertension and Renal Center of Excellence, Tulane University Health Sciences Center, 1430 Tulane Avenue, New Orleans, LA 70112, USA

Correspondence should be addressed to Ihor V. Yosypiv, iiosipi@tulane.edu

Received 25 November 2010; Revised 8 January 2011; Accepted 15 January 2011

Academic Editor: Karl Matter

Copyright © 2011 Renfang Song et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The kidney plays a fundamental role in the regulation of arterial blood pressure and fluid/electrolyte homeostasis. As congenital anomalies of the kidney and urinary tract (CAKUT) constitute one of the most common human birth defects, improved understanding of the cellular and molecular mechanisms that lead to CAKUT is critical. Accumulating evidence indicates that aberrant signaling *via* receptor tyrosine kinases (RTKs) is causally linked to CAKUT. Upon activation by their ligands, RTKs dimerize, undergo autophosphorylation on specific tyrosine residues, and interact with adaptor proteins to activate intracellular signal transduction pathways that regulate diverse cell behaviours such as cell proliferation, survival, and movement. Here, we review the current understanding of role of RTKs and their downstream signaling pathways in the pathogenesis of CAKUT.

Pediatr Nephrol. 2014 April ; 29(4): 597–608. doi:10.1007/s00467-013-2606-5.

To Bud or not to Bud: The RET perspective in CAKUT

T. Keefe Davis[1], **Masato Hoshi**[2], and **Sanjay Jain**[2,3,*]

[1]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110, USA

[2]Department of Internal Medicine (Renal division), Washington University School of Medicine, St. Louis, MO 63110, USA

[3]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA

Abstract

Congenital anomalies of the kidneys or lower urinary tract (CAKUT) encompass a spectrum of anomalies that result from aberrations in spatio-temporal regulation of genetic, epigenetic, environmental and molecular signals at key stages of urinary tract development. The Rearranged in Transfection (RET) tyrosine kinase signaling system is a major pathway required for normal development of the kidneys, ureters, peripheral and enteric nervous systems. In the kidneys, RET is activated by interaction with the ligand glial cell line-derived neurotrophic factor (GDNF) and coreceptor GFRα1. This activated complex regulates a number of downstream signaling cascades (PLCγ, MAPK and PI3K) that control proliferation, migration, renewal and apoptosis. Disruption of these events is thought to underlie diseases arising from aberrant RET signaling. *RET* mutations are found in 5–30% of CAKUT patients and a number of Ret mouse mutants show a spectrum of kidney and lower urinary tract defects reminiscent of CAKUT in humans. The remarkable similarities between mouse and human kidney development and in defects due to *RET* mutations has led to using RET signaling as a paradigm to determine the fundamental principles in patterning of the upper and lower urinary tract and to understand CAKUT pathogenesis. In this review we provide an overview of studies in vivo that delineate expression and the functional importance of RET signaling complex during different stages of development of the upper and lower urinary tracts. We discuss how RET signaling balances activating and inhibitory signals emanating from its docking tyrosines and its interaction with upstream and downstream regulators to precisely modulate different aspects of Wolffian duct patterning and branching morphogenesis. We outline the diversity of cellular mechanisms regulated by RET, disruption of which causes malformations ranging from renal agenesis to multicystic dysplastic kidneys in the upper tract and vesicoureteral reflux or ureteropelvic junction obstruction in the lower tract.

NIH Public Access
Author Manuscript
Pediatr Nephrol. Author manuscript; available in PMC 2015 April 01.

Published in final edited form as:
Pediatr Nephrol. 2014 April ; 29(4): 565–574. doi:10.1007/s00467-013-2599-0.

MicroRNAs: potential regulators of renal development genes that contribute to CAKUT

April K. Marrone[1] and **Jacqueline Ho**[1]

[1]Division of Nephrology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15224, USA

Abstract

Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of childhood chronic kidney disease (CKD). While mutations in several renal development genes have been identified as causes for CAKUT, most cases have not yet been linked to known mutations. Furthermore, the genotype-phenotype correlation is variable, suggesting that there are additional factors that impact the severity of CAKUT. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level, and are involved in many developmental processes. Although little is known about the function of specific miRNAs in kidney development, several have recently been shown to regulate the expression of, and/or are regulated by, crucial renal development genes present in other organ systems. In this review, we discuss how miRNA regulation of common developmental signaling pathways may be applicable to renal development. We focus on genes that are known to contribute to CAKUT in humans, for which miRNA interactions in other contexts have been identified, with miRNAs that are present in the kidney. We hypothesize that miRNA-mediated processes play a role in kidney development through similar mechanisms, and speculate that genotypic variations in these small RNAs or their targets could be associated with CAKUT.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

miRNA'lar

- Tek gen kalıtımı
  - Fenotip genotip farkı
- Pek çok genin işlevinde rolü
  - TGFbeta, EYA1, GDNF, SIX1, SOX17…
- RAS'ta rolü

Sonuç

(Eve götüreceklerimiz)

- İzole/sendromun parçası
- Patogenezde genetik
  - Tek gen birkaç anomali,

    tek anomali birkaç gen
  - Genetik danışma?
  - Aile taraması!!!
- Patogenezde yol alma→ Korunma ve tedavi

Sabrınız için teşekkürler