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Genetic Basis of Ureterocele

Karin Schultz[a,*] and Lia Yoneka Toda[b]

[a]*Department of Urology, Hospital Pequeno Principe, Curitiba, Parana, Brazil;* [b]*Department of Pediatric Surgery, Universidade Estadual de Maringa, Hospital Universitário de Maringa, Maringa, Parana, Brazil*

K. Schultz

Abstract: Congenital anomalies of the kidney and urinary tract (CAKUT) form a group of heterogeneous disorders that affect the kidneys, ureters and bladder, with frequent asynchronous presentations and multiple CAKUT associations in the same individual. Urinary tract formation is a complex process, dependent of the interaction of multiple genes and their sub-product. The same genic alterations can lead to different molecular expressions and different morphological anomalies. The ureterocele is a cystic dilation of the distal intramural ureter, resulting in obstruction of urine flow, dilation of the ureter and renal pelvis and loss of renal function. Two key steps in the urinary tract ontogenesis may be related to ureterocele development: formation and migration of the ureteric bud and its incorporation in the bladder. This review aims to describe the morphological, cellular and biochemical steps, as well as the genes involved in the occurrence of this anomaly.

Keywords: CAKUT, Genetic basis, Ureterocele, Urologic ontogenesis.

1. INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) form a group of heterogeneous disorders that affect the kidneys, ureters and bladder. In this group are included common problems such as vesicoureteral reflux to severe life-threatening malformations as bilateral renal agenesis [1-4].

In young children, CAKUT are the main cause of end-stage kidney disease, leading to the need for kidney transplantation or dialysis, causing major impact on growth, maturation, and disturbed cognitive development and leading to a poor life expectancy [5, 6]. The survival rate of this group is 30 times lower than that of healthy children [5]. It may be also associated with kidney problems in latter life, such as hypertension and proteinuria [7]. CAKUT has also a significant economic impact on health care systems because of the patients lifelong costly therapeutic needs and impact of the employment potential of affected individuals and their families [5].

They are present in 0.5 to 0.6% of gestations [1, 3, 8, 9], accounting for 20 to 30% of all congenital anomalies detected in the neonatal period [3, 10, 11]. This is a group diseases with an inherited polygenic trait, in addition to variable and incomplete penetrance, of multifactorial order, and can be related to de novo mutations, exposure to teratogenic substances, and maternal diet [12]. The development of the urinary tract depends on a series of complex events derived from several genic products (transcription factors, growth factors, receptors) necessary to the distinct stages of organogenesis [13]. Recent progresses in the understanding of the origins of urinary tract development in mice and other animals suggest a new picture to the interpretation of these defects in humans [3, 14]. Genetic manipulations in mice identified a number of genes and genes network that direct the normal development of kidney and urinary tract, providing a new insight into the pathogenesis of CAKUT [1, 3, 15-17]. A list of these can be found in a database available online (www.gudmap.org, www.omin.org). Few of these studies will be mentioned latter through this paper.

The intrauterine environment has been linked to CAKUT. The mechanistic basis for CAKUT associated with altered intra-uterine environment remains to be elucidated further. Maternal history of use of alcohol and drugs (cocaine) during pregnancy is related to the occurrence of CAKUT [18, 19]. A low-protein maternal diet during early pregnancy in mice could affect the expression of renal developmental genes (RDG) in the embryonic metanephros, reducing nephron number and causing renal hypoplasia [20]. Two different mechanisms could be involved in this: low- protein levels lead to increase concentration of glucocorticoids via down-regulation of the placental steroid- metabolizing enzyme 11β-hydroxysteroid dehydrogenase type2 [21], or causes down-regulation of angiotensin II contents in the embryonic kidney [20, 21]. Both excessively high and low maternal sodium intake during pregnancy in the rat cause aberrant expression of critical RDGs and reduce the final number of glomeruli in the off-spring, predisposing to hypertension later in life [22]. Rats with deficiency of bradykinin B2 receptor exposed to an excessive sodium intake during gestation develop kidney hypodisplasia, demonstrating the principle that environmental factors may act together with mutations of a single gene in the genesis of CAKUT [23].

*Address correspondence to this author at the Department of Urology, Hospital Pequeno Principe, Faculdades Pequeno Principe, Departamento de Medicina, Av Iguaçu, 333, Rebouças, Curitiba, PR, Brazil, 80230-020; Tel: 55 41 88460459; Fax: 55 41 33101500;
E-mails: karinschultz@yahoo.com; karinluschultz@gmail.com

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Recent studies [1, 3, 4, 11-13, 20-22] have also steps and cause a broad phenotypic of CAKUT [1, 3, 24] proved that the very same genes responsible for the initial Syndromic forms of CAKUT occur in the context formation of urinary tract organs would also regulate later of multiorgan malformation (outside urogenital system) phases of the process, explaining the broad spectrum of [1, 2]. Genetic causes have been identified for the syndromic existing CAKUT, as well as different bilateral manifestations forms and have shed some light into the molecular in a same individual. (Table **1**). The action of different mechanisms of kidney development in human beings [2]. genes in kidney development with inducing effects in 10% of patients with syndromic CAKUT will carry DNA various tissues, such mesenchyme, ureteric bud and cloaca, micro imbalances, and four chromosomal regions acting in different ontogenic stages is necessary for normal presumably associated with the CAKUT phenotype were morphogenesis of kidney and urinary tract [24]. A single identified: 1q21.1, 2q37, 1-q37.3, 3q23-q25.1 and 7q36.2- gene mutation might affect kidney development at multiple q36.3 [25].

PAX2, a paired-box transcription factor, has been identified as the responsible gene whose mutation is associated with the subgroup of CAKUT seen in the renal-coloboma Syndrome [26]. PAX2 is required for the growth and elongation of Nefric duct (ND) prior to ureteral budding [3]. Bronchio-oto-renal syndrome (BOR) is a dominantly inherited disorder. BOR's patients presents abnormalities of all parts of the ear associated with conductive, sensorineural, or mixed hearing impairment, branchial fistulae and cysts, and different CAKUT manifestations [27, 28]. BOR is linked to haploinsufficiency for EYA1, a homolog of *Drosophila melanogaster* gene eyes absent (eya) [28-30]. Molecular genning testing for EYA1 detects mutations in approximately 40% of individuals with the clinical diagnosis of BOR [31].

The genetic cause for the most common forms of non-syndromic CAKUT are unknown. In non-syndromic form of CAKUT the structural anomalies are confined only to the kidney and urinary tract. The causes for the non-syndromic CAKUT types are considered multifactorial, resulting from the combination of epigenetic and environmental factors that affect genetically susceptible individuals [1, 3]. Only few genes [32, 33] has been implicated as responsible for non-syndromic causes of human CAKUT (Table **1**).

Renal abnormalities are also observed in close relatives of up to 10% of CAKUT patients, although these are frequently asymptomatic. There are related cases of familial ureterocele, renal agenesis, hypodysplasia, renal tubular dysgenesis, multicystic dysplastic kidney (MCDK), or VUR [34-38]. The phenotype often does not follow the classic Mendelian inheritance: family members with the same genetic defect may have variable phenotypes, ranging from severe renal insufficiency to asymptomatic anomalies. The occurrence of several presentations CAKUT in the same family indicates the possibility that a specific genetic mutation can lead to abnormalities in the development of urinary tract, however the final renal phenotype depends on both genetic background and environmental factors [1, 3].

Ureterocele

Ureterocele is an example of CAKUT. It is a cystic outpouching of the distal ureter into the urinary bladder [34, 39] (Figs. **1-3**). Ureteroceles can be a diagnostic and therapeutic challenge with clinical symptoms arising from an abnormal spectrum embryogenesis mainly associated with the abnormal development of the ureteral intravesical.

They may be asymptomatic or appear with a wide range of clinical signs and symptoms, from recurrent urinary tract infection to bladder outlet obstruction and renal failure. Ureterocele usually causes obstruction of the affected renal unit and can be associated with varying degrees of dilatation of the renal pelvis and ureter, with or without the loss of kidney function [39]. Ureteroceles can be categorized based on their relationship with the renal unit or on the distal ureteral configuration and location (Table **2**). Several forms of ureterocele classification have been proposed throughout the years, and the most popular one was established by the American Academy of Pediatrics in 1984 [34, 40]. The orthotopic or intravesical ureterocele is entirely located inside the bladder, whereas the ectopic has a portion permanently situated in the vesical neck or in the urethra. Double-system ureterocele is associated with the upper pole of a kidney with complete collecting system duplicity, whereas single-system ureterocele is associated with a kidney with one single ureter. This classification of ureteroceles is useful in determining the type of treatment proposed and defining prognosis, especially with respect to the likelihood of the presence of bladder neck obstruction or occurrence of vesicoureteral reflux after treatment transurethral puncture [39, 40].

Ureteroceles occur in approximately 1 in every 4000 children and are most common in whites. Their postmortem incidence is 1 in 500 – 4000 [34]. Ureteroceles are more frequent in female patients (4-6 times more common). In the adult population, ureteroceles also occur more frequently in females. The laterality shows a slight predominance on the left side, with near 10% bilateral disease. Orthotopic ureteroceles occur in 17-35% of cases, with an incidence of ectopic ureteroceles of approximately 80% in most pediatric series. 80% of ureteroceles are associated with the upper pole moiety of a duplex system. In these cases, the upper pole tends to be dysplastic or poorly functioning. Single-system ectopic ureteroceles are uncommon and most often found in males [34, 39].

Series of family cases of ureterocele are described [34, 41-44] in both single and double systems, suggesting the possibility of genetic predisposition. The first description of family cases of ureterocele was made in 1939: simple system ureterocele in 29 years old identical twins [41]. In 1980 was observed cases of the malformation in teenager siblings [43]. A year earlier a family series was reported: dizygotic brothers affected by ureterocele, their parents are first cousins and the father and a sister had double collecting system [44]. By 2005, there were around 10 families registered with multiple cases of ureterocele [34].

There is a small number of specific studies on its genetic causes, most part of which groups this anomaly with other CAKUT. It is probable that most CAKUT are examples of complex hereditary traits resulting from smaller mutations of

Table 1. Gene mutation linked to CAKUT associated with the disease name in the database of the online mendelian inheritance in man (OMIM®), chromosomal locus and renal and extra-renal phenotype (Resumed and adapted from [1]).

Gene	Disease OMIM(*)	Chromosome	Renal Phenotype	Extrarenal Phenotype
AGT	Renal tubular dysgenesis (RTD)	1p42	Reduced number of proximal tubules, short proximal tubules without brush border, atrophic loops of Henle and collecting ducts, closely packed glomeruli, marked thickening and disorganization of interlobular and preglomerular arteries	Large low-set ears, limb-positioning defects, arthrogryposis, lung hypoplasia, skull ossification defects
AGTR1	Renal tubular dysgenesis (RTD)	3p24	Similar to AGT phenotype, PUV	Similar to AGT phenotype
AGTR2	—	Xq22-q23	UPJ obstruction, megaureter, MCDK hydronephrosis, PUV	—
ACE	Renal tubular dysgenesis (RTD)	17q23.3	Similar to AGT phenotype renal hypodysplasia, PUV	Similar to AGT phenotype
BMP4	—	14q22-q23	Renal hypodysplasia	Cleft lip, microphthalmia
BMP7 Dlx5/Dlx6p63	Split Hand/foot malformation (SHFM)	3q27	Urethral malformations	Split-hand/split-foot malformation
CDC5L	—	46XX,t(6; 19) (p21; q13.1)	Multicystic kidney dysplasia	—
Eya1	Branchio-oto-renal syndrome (BOR)	8q12	Unilateral or bilateral renal agenesis renal hypodysplasia, VUR	Deafness, ear malformations branchial cysts
Fras1/ Fram2	Fraser syndrome	4q2113q13. 3	Renal agenesis/hypodysplasia	Ear and heart defects, syndactyly cryptophthalmos
FoxC1	—	6p25	CAKUT	—
Gata3	Hypoparathyroidism, sensorineural deafness, and renal disease syndrome (HDR)	10pter	Renal dysplasia	Hypoparathyroidism sensorineural deafness
HNF1β/ TCF2	Maturity-onset diabetes of the young (MODY5)Renal cysts and diabetes syndrome (RCAD)Glomerulocystic kidney disease (GCKD)	17q12	Renal hypodysplasia, cysts	Diabetes
Pax2	Renal-colobomasyndrome	10q24	Renal hypoplasia, VUR	Optic nerve coloboma branchyal cysts
Ren	Renal tubular dysgenesis (RTD)	17q23.3	Similar to AGT phenotype	Similar to AGT phenotype
Ret	Renal agenesis	10q11.2	Absence of the kidney and ureter	Hirschsprung disease
Robo2	—	3p12.3	VUR	Limb and facial defects
Six2	—	2p16-p15	Renal hypodysplasia	—
Slit2	—	4p15.2	Hydroureter, supernumerary UBs	—
Umod	Medullary cystic kidney disease (MCDK2)	16p12.3	Cysts in distal tubules and collecting ducts, renal dysplasia	—

(Table 1) contd….

Gene	Disease OMIM(*)	Chromosome	Renal Phenotype	Extrarenal Phenotype
Upk3A	—	22q13.31	Renal agen-esis/hypodysplasia	Facial and limb defects
Usf2	—	46XX t(6;19) (p21; q13.1)	Multicystic kidney dysplasia	—
XPNPEP3	Nephronophthisis (NPHP) -like nephropathy	22q13.2	Renal cysts and dysplasia	—

Abbreviations: AGTR: angiotensin II receptor type 1, AGTR2: angiotensin II receptor type 2, ARPKD: autosomal-recessive polycystic kidney disease, ADPKD: autosomal-dominant polycystic kidney disease, UPJ: ureteropelvic junction, VUR: vesicoureteral reflux, PUV: posterior urethral valves, UPJ: ureteropelvic junction, MCDK: multicystic dysplastic kidney, RTD: renal tubular dysgenesis.

multiple specific genes that are involved in the normal development of the urinary tract [45].

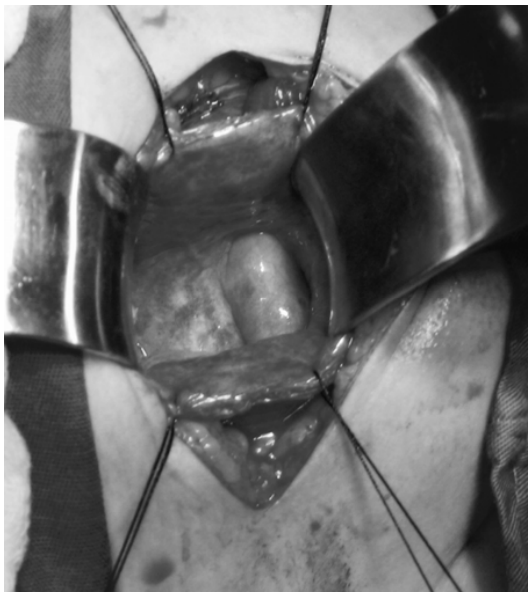

Fig. (1). Surgical view of an opened bladder demonstrating a left-sided ureterocele.

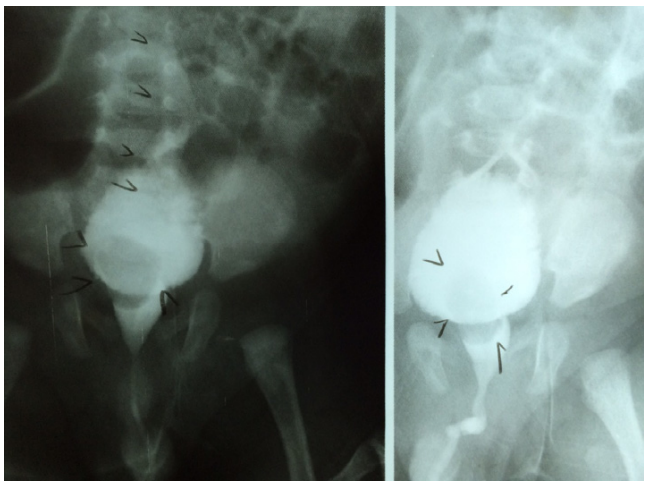

Fig. (2). Retrograde voiding uretrocistography showing a large right-side ureterocele prolapsing into the bladder neck.

Two fundamental steps in ureter and bladder embryogenesis can be related to the ureterocele development, described by [46] as "pipe installation" (development of the nephric duct (ND) or Wolfian duct and of the ureteric bud) and "plumbing" (distal ureter maturation and consequent incorporation in the bladder). Both are strongly linked to ureterocele development in both single and double systems. [46].

This work aims to review the morphological and molecular stages of, as well as genetic abnormalities possibly related to ureterocele development.

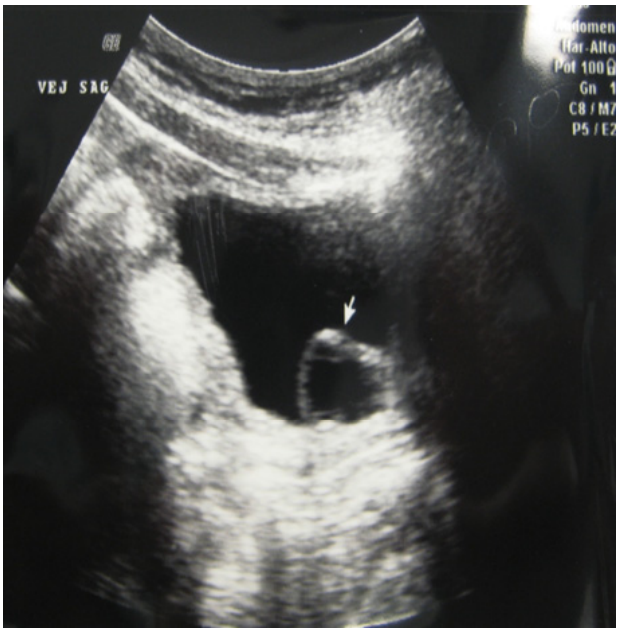

Fig. (3). Ultrasound showing the cystic formation inside the bladder (arrow) that is the ureterocele.

Mesonephric Duct and Ureteric Bud Formation

The upper urinary tract (kidneys and ureters) has an ontological origin completely different from that of the lower tract (bladder and urethra), and the perfect coupling of the two units is fundamental to allow a functional urinary flow [47]. The ureter originates as a ND epithelial protrusion that extends throughout the intermediate mesoderm at the level of the forelimb until the cloacal plate [48, 49]. The proximal portion of the bud invades the metanephric blastema, starts a

successive elongation and bifurcation process, generating the renal collecting system. The branch, in turn, (bud portion located outside the metanephrine) merely elongates until reaching the urethral plate [47]. The metanephric mesenchyme of the upper portion of the ureter forms the nephrons and the renal stroma [50]. The distal mesenchyme has a smooth muscle with layers of longitudinal and cross-sectional orientation, forming the ureteral wall [47].

Table 2. Terminology for duplex systems, ectopic ureters and ureteroceles [40].

Colector System	Ureteral Ostium Position
Single system	Orthotopic
Duplex system	Ectopic

The ectopy of the ureteric bud is considered the first false step that leads to several urogenital anomalies. The formation process of the bud is not guided by the intrinsic position of the ND, but rather by signalers of the adjacent mesenchyme [47, 51]. The formation of a unique and properly located ureteric bud critically depends on the correct expression of the GNDF (Glial-derived neurotrophic factor), which is produced by the metanephric tissue and couples with the c-ret tyrosine kinase receptor (Ret/GFRα1), with subsequent activation of several intracellular pathways leading to cellular shape changes, proliferation, migration and adherence to the epithelium of the adjacent ND, inducing the formation of the ureteric bud [47, 48, 52]. In humans, Ret gene mutations are associated with the Hirschsprung disease, neoplasia, and urinary tract anomalies; similar alterations are found in mice [52].

The total or partial loss of the GNDF signaling network results in emergence and growth failure of the ureteric bud, leading to renal agenesis or severe hypoplasia [49, 53]. Hyperexpression leads to the formation of two or more ureteric buds, whereas anomalous spatial expression causes formation to occur earlier or later than usual, which is translated in the ectopic implantation of the ureter in the bladder or urethra [46, 48, 49]. This is in agreement with the "Bud Theory" observed through extensive inspections of embryos and neonates. This theory observes morphological correlations between the location of the ureteral orifice, renal dysplasia degree and ureter abnormalities [3]. A ureter rostral bud would be inserted last and in a low position in the bladder neck, in the urethra or in the sexual ducts, presenting an obstructive pattern, and may or may not be associated with ureterocele. A caudal ureteric bud would be inserted in the upper position, with early incorporation in the cloacal plate, a more lateral and cranial migration, less trigonal support and a short mesenchyme tunnel, being associated with vesical reflux. The clinical observation of the Weigert-Meyer law supports this theory; the duplex upper pole stands in a lower position, a generally obstructive pattern, whereas the lower pole opens in the upper side and is associated with vesicoureteral reflux [34, 46].

The GDNF expression is regulated by a network of several genes and transcription factors [49]. The Osr1 gene regulates the activation of transcriptional factors such as Eya1, Pax2, Sall1. Proteins like Slit2 and its Robo2 receptor, and transcription factors like FoxC1 and FoxC2 are responsible for the repression of the GNDF action in the rostral mesenchyme adjacent to the ND. Ablation of signaling system codifier genes of FoxC1 and FoxC2 transcription factors by Slit 2 protein and its homologous receptor Robo2 in the mesenchyme adjacent to the ND results in the spatial expansion of the metanephric blastema and of the activity area of GNDF signals, with formation of multiple ureteric buds and ectopic ureters [49]. FoxC1 homozygotes have an accessory ectopic bud, witch emerges more cranially from ND, usually enlarged and with ectopic distal connections [3].

The Gata3 gene transcription factor regulates the Ret activation through β-catenin signaling. A combined mutation of β-catenin and Gata3 leads to Ret expression loss in mice embryos, but the β-catenin expression is not affected by lack of Gata3, suggesting a supra-regulation process with a β-catenin–Gata3–Ret cascade in the ND. In addition, the maintenance of the Ret expression after the formation of the ureteric bud seems to be dependent of additional transcription factors as Lim1 and Emx2 and signaling through retinoic acid [46]. In mice, Gata3 gene inactivation leads to defects in the proliferation of renal ducts, besides leading to premature differentiation of renal duct cells. In humans, Gata3 gene functional loss is associated with the Barakat syndrome, characterized by hypoparathyroidism, deafness, renal dysplasia/agenesis and vesicoureteral reflux [54].

Angiotensin type 2 receptor gene (Agtr2) prevent aberrant ureter budding from the ND. Rodents inactivated by genetic engineering for Agtr2 had an initial rate of 2-3% of CAKUT, the penetrance was increased to almost 20% afters sequential cross breeding, indicating that this anomaly is also regulated by another gene (s). Agtr2 null mutants care ectopic budding and many carry a duplex system. Circa half of the mutants embryos showed abnormal initial budding either as two distinct buds or as one larger and broader bud relative to normal [3]. The BMP4 gene (bone morphogenic protein 4), through the BMP4 activation molecule, serves as an inhibition factor to the GNDF-ret signaler bud inductor, probably determining a new bud formation site [3, 55].

BMP4 serves as an inhibitory factor for the bud-inducing GDNF-ret signaling along the ND and the stalk of ureter, thereby determining the site of new bud formation.

The inhibiting effect of the BMP4 in the ureteric bud is inhibited by the secretion of the Gremlin protein in the ureteric bud, allowing the localized expression of the GNDF/Ret network and the growth of the ureteric bud [47]. BMP4 functional defects in mice (Bmp4 +/-) generate ectopic or accessory ureteric bud, leading to different types of CAKUT, whereas homozygosis (Bmp4 -/-) is always lethal [3, 53]. Moreover, the BMP4 also acts as a signaler in smooth muscle and, possibly, in urothelium differentiation, in addition to acting in the mesenchyme of the lower urinary tract, activating regional transcriptional systems. Absorption and modulation failures of the mesenchymal tissue of the distal ureter and bladder could justify the occurrence of weakness in the vesical wall and subsequent dilation with ureterocele formation [47]. The diverse and prolonged activity of the BMP4 gene in the urinary tract morphogenesis could justify the multiple and different phenotypes observed in humans with BMP4 gene mutation [56].

Maturation of the Distal Ureter and its Incorporation in the Bladder

This process consists of the mobilization of the distal portion of the ureteric bud until its ending position at the vesical wall. The distal part of the ureter has to be translocated from the ND to the developing bladder wall [8, 11, 47].

After the initial contact of the mesonephric duct with the cloacal plate, the structures fuse. Recent studies show that there is no incorporation of the distal part in the primordial bladder tissue, but a ND apoptosis process that promotes direct contact between the epithelium of the ureteric bud and the epithelium of the cloacal plate [54]. At this stage, the ureter suffers an 180-degrees rotation around the ND axis, forming a new connection point from the ureter to the bladder, causing the loss of contact with the ND and consequent spatial incorporation inside the bladder (formation of the submucous tunnel and vesical trigone) [11].

The apoptosis and remodeling mechanism of the ND and ureteric bud requires the expression of the Lar-family-receptor (Leukocyte common antigen-related family receptor protein tyrosine phosphatases) through the LAR-RPs, RPTPσ and LAR enzymes and their PTRF and S receptors, [11, 46] which act in the down-regulation process of the Ret chain. The perfect balance of the LAR-RTPP proapoptotic action and of the Ret prosurvival action determines the correct position of the ureter in the bladder [57].

Retinoic acid and receptors for PTPRF and PTPRS tyrosine kinase act in Ret activity control at the transcriptional and proteinic levels, respectively.

Retinoic acid (vitamin A active form), a key substance in the embryo morphogenesis, activates transcription pathways. Mutations in the Aldh1a2 (also called Aldh1a2), main synthesis enzyme of the retinoic acid, retinoic acid signaling loss and/or vitamin A deficiency are associated with hydronephrosis, megaureter and ureteral ectopy [52]. The complete elimination of the acid retinoic activity, whether by elimination of the RARa/RARb or Aldh1a2 receptor genes in the mesenchyme surrounding the mesonephric duct, results in the absence of distal ureter apoptosis, in addition to down-regulation in Ret expression in the ND. The retinoic acid action in the developing bladder is triggered by the up-regulation of cellular retinoic acid binding protein, retinoic acid early transcription 1α and retinoic acid receptor-β. There is also the up-regulation of genes associated with cellular maturation, as Mdk (heparin binding growth factor), also induced by retinoic acid action. Mdk acts in angiogenesis, cellular differentiation, mesenchyme-epithelium interaction, and nervous system maturation [58].

Mutant mice for Rara, Rarb2 and Aldh1a2 genes, and animals with inactivation of receptors for PTPRF and PTPRS tyrosine kinase present retinoic acid synthesis failures, with flaws in the apoptosis process of the ND, distal ectopic connection of the ureter to the vesical neck or urethra, and obstruction of the urine normal flow in the affected kidney. In PTPRF;PTPRS double mutants, there is a decrease of more than 80% in apoptosis rates, which leads to delayed ureteral maturation, and the resulting obstruction commonly leads to ureterocele formation [5, 20, 25]. In mice with Aldh1a2 deficiency, hydronephrosis and hydroureter not associated with ureterocele formation usually occur. The deletion of Aldh1a2 from the mesenchyme leads to a signaling reduction of RaRA, RARb and Raldg2 receptors, with a decrease in Ret expression in the ND. The complete ablation of the Aldh1a2 activity is enough to eliminate completely the apoptosis process of the ND [11, 59].

In short, the migration and insertion of the ND and ureteric bud depend on Ret activity and Ret expression, and is mediated by the action of the retinoic acid and Gata3. This communication pathway is crucial for the maturation of the distal ureter of the bladder.

CONCLUSION

Urinary tract formation is a complex process, dependent of the interaction of multiple genes and their sub-product. The same genic alterations can lead to different molecular expressions and different morphological anomalies. Ureterocele is one of these anomalies, and its occurrence may be related to the initial formation process of the ureter, its migration and incorporation to the cloacal plate, being resulting from interaction of innumerous morphological, cellular and biochemical factors. The genetic causes for ureterocele and other form of CAKUT are unknown. Further studies are necessary for a complete elucidation of its occurrence. The collaboration of several multidisciplinary research centers worldwide is necessary to discover the molecular and genetic pathogenesis of CAKUT, improving care for patients and their families by performing personalized medical treatment based on detailed understanding of the molecular pathogenesis of the disease, early diagnosis strategies, monitoring and treatment.

CONFLICT OF INTEREST

The authors declare absence of financial contributions and any potential conflict of interest.

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