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Lower urinary tract development and disease

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Abstract

Congenital Anomalies of the Lower Urinary Tract (CALUT) are a family of birth defects of the ureter, the bladder and the urethra. CALUT includes ureteral anomalies such as congenital abnormalities of the ureteropelvic junction (UPJ) and ureterovesical junction (UVJ), and birth defects of the bladder and the urethra such as bladder-exstrophy-epispadias complex (BEEC), prune belly syndrome (PBS), and posterior urethral valves (PUV). CALUT is one of the most common birth defects and is often associated with antenatal hydronephrosis, vesicoureteral reflux (VUR), urinary tract obstruction, urinary tract infections (UTI), chronic kidney disease and renal failure in children. Here, we discuss the current genetic and molecular knowledge about lower urinary tract development and genetic basis of CALUT in both human and mouse models. We provide an overview of the developmental processes leading to the formation of the ureter, bladder, and urethra, and different genes and signaling pathways controlling these developmental processes. Human genetic disorders that affect the ureter, bladder and urethra and associated gene mutations are also presented. As we are entering the post-genomic era of personalized medicine, information in this article may provide useful interpretation for the genetic and genomic test results collected from patients with lower urinary tract birth defects. With evidence-based interpretations, clinicians may provide more effective personalized therapies to patients and genetic counseling for their families.

INTRODUCTION

Each year an estimated six percent of total births worldwide (~ 8 million children) including three percent of all live births in the United States (more than 120,000 babies) are born with a serious birth defect of genetic origin.[1–3] Among these, as many as one percent of human fetuses have congenital anomalies of the kidney and urinary tract (CAKUT), which is a family of birth defects including kidney anomalies such as renal hypodysplasia and hydronephrosis, and lower urinary tract (LUT) anomalies such as vesicoureteral reflux (VUR), urinary tract obstruction, bladder and urethral abnormalities.[4–6] Although CAKUT is a complex genetically heterogeneous developmental disorder with variable phenotype, it can be caused by mutations in a single gene that controls early kidney and lower urinary tract development.[7–11] CAKUT is a leading cause of urinary tract infection (UTI), chronic kidney disease and renal failure in children and may also manifests as primary renal disease in adults as more children with urinary tract birth defects survive to adulthood.[12–14] However, little is known about the contribution of congenital lower urinary tract malformations to chronic kidney disease and renal failure in CAKUT patients as we lack a comprehensive understanding of the genetic and molecular basis of the lower urinary tract development. Therefore, it is challenging to provide genetic counseling, molecular

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diagnosis, and personalized medical/surgical management to patients with these broad clinical conditions without a clear understanding of their developmental etiology.[15, 16]

The urinary system is a multi-component organ system, whose primary function is to produce, transport, store, and eliminate urine in order to maintain body homoeostasis by controlling the water and ionic balance of the blood. Anatomically, these functions are served by an upper unit, the kidney, which filters and modifies the blood to produce urine, and a lower unit consisting of the ureter, the bladder, and the urethra, which transports, stores and eliminates the urine to the outside. Normal development of the upper unit kidney and associated congenital renal anomalies have been well reviewed recently[17–23]. In this article, we focus on current genetic and molecular knowledge of lower urinary tract development and related birth defects of the ureter, the bladder and the urethra in both human and mouse models, which are collectively named CALUT (Congenital Anomalies of the Lower Urinary Tract) in this review. We will describe different molecular pathways controlling lower urinary tract development as well as human genetic disorders affecting the lower urinary tract. We believe that understanding the genetic basis of CALUT in patients can help scientists and clinicians to decipher the molecular mechanism of normal developmental processes of the lower urinary tract and discover more CALUT causative genes.

OVERVIEW OF LOWER URINARY TRACT DEVELOPMENT

Development of the ureter and ureteral peristaltic machinery

The kidney and ureter share a common ontogenic origin, the intermediate mesoderm, in early embryos when an epithelial outpouching called the ureteric bud (UB) sprouts from the caudal region of the Wolffian duct (also called mesonephric duct) and invades adjacent metanephric mesenchyme (MM) (Figure 1A). This process begins at around 4 weeks of gestation in human and at embryonic 10.5 days (E10.5) in mouse. After the ureteric bud invasion into the metanephric mesenchyme, the reciprocal interaction between the tip of the ureteric bud and the metanephric mesenchyme results in multiple rounds of UB branching morphogenesis to form the collecting system, while mesenchymal-to-epithelial transition (MET) of the MM leads to the formation of the nephron.[24] These developmental processes ultimately give rise to a functional kidney that starts to produce urine at ~10 weeks of gestation in human and at ~E16.5 in mice. At the same time, the trunk of the ureteric bud (i.e. the UB portion remaining outside of the metanephric mesenchyme) gains a different fate and elongates without branching to form the ureter, a muscular tube structure transporting urine from the kidney to the bladder (Figure 1B, 1C).[25] Together with the growth of the caudal part of the body during fetal development, the elongation of the ureter leads the ascent of the kidney to its final position at the level of upper lumber vertebrae.

Similar to the kidney development that is guided by the reciprocal interaction between the epithelial cells in the UB tips and the mesenchymal cells in the MM, the morphogenesis of the ureter also requires a close interaction between the inner ureteral epithelial cells and the surrounding ureteral mesenchymal cells. In response to the molecular signals from the ureteral epithelial and mesenchymal cells, the early simple cuboidal ureteral epithelial cells differentiate into the multilayered urothelium (also called transitional epithelium, a part of mucosa after maturation). The urothelium is covered by urothelial plaques expressing uroplakin proteins and is impermeable to urine and its caustic effect.[26–28] This process occurs around 10 weeks in human and E16.5 in mouse, which coincides with the beginning of urine production by the embryonic kidney. Meanwhile, the mesenchymal cells differentiate into the stromal cells, smooth muscle cells, and adventitial fibroblasts (also called serosa after maturation) (Figure 1D). Differentiated smooth muscle cells are further organized into layers with inner circular and outer longitudinal orientation, and are

characterized with strong expression of α-smooth muscle actin.[29–32] Interestingly, the ureter smooth muscle differentiation occurs in an ascending fashion from the distal ureter close to the bladder (i.e. ureterovesical junction - UVJ) to the proximal ureter that is next to the intrarenal collecting system (i.e. ureteropelvic junction - UPJ).[30] This developmental process is in the opposite direction to the propagation of ureteral peristaltic waves that transport urine from the kidney to the bladder (Figure 1C).

Ureteral peristaltic waves are initiated in the renal pelvis and are propagated rhythmically through the ureter wall to the bladder. This contractile activity is triggered by special pacemaker cells located in the most proximal calyceal region of the pelvic-kidney junction, which produces regular pulsatile electrical signals transmitted along the electrically active "typical" smooth muscle cells (Typical SMC) in the ureter.[33] Two types of special pacemaker cells with electrical rhythmicity have been identified in the renal pelvis and ureter. The primary pacemaker cells are also called "atypical" smooth muscle cells (Atypical SMC) because they contain fewer contractile filaments with weak α-smooth muscle actin expression compared to the regular "typical" smooth muscle cells that are most abundant in the ureter. Atypical SMCs are mainly located within the most proximal region of the renal pelvis and have many morphological features similar to those of the cardiac sinoatrial pacemaker cells.[34] The other type of pacemaker cells in the renal pelvis and ureter is the interstitial cells of Cajal (ICC) – like cells (ICC-LCs), which are characterized by the expression of the proto-oncogene Kit and have thin and long cytoplasmic processes that are similar to those of the intestinal ICCs.[35, 36] These ICC-LCs are located sparsely throughout the ureter (including renal pelvis, UPJ, UVJ), and among atypical SMCs, typical SMC (including inner circular and outer longitudinal muscle layers), the lamina propria underneath the urothelium, and neurons.[36, 37] However, the distribution of ICC-LCs is not even, with most ICC-LCs located in the proximal renal pelvis and reduced cell density in the distal segments of the ureter.[36, 37] The ICC-LCs can produce electrical slow-wave potentials that control the propagation of the unidirectional ureteral peristaltic activity.[37]

The molecular mechanism and physiological functions of the ureteral peristaltic machinery are still ill-defined. It has been suggested that atypical SMCs in the tip of renal pelvis act as the primary pacemaker to initiate spontaneous transient potentials that are propagated and modulated by ICC-LCs to the adjacent typical SMCs in order to trigger intermediate action potentials and ureteral smooth muscle contraction. The ICC-LCs may also produce additional autorhythmicity and can take over pacemaking in the renal pelvis and ureter in the absence of the primary pacemaker activity from the atypical SMCs.[37, 38] The development of the ureteral peristaltic machinery is also not well understood. A recent study shows that mouse Kit-expressing ICC-LCs are first detected at E15.5 in a subset of renal epithelial cells and cells of the ureteropelvic adventitia.[35] This developmental time point is followed by the beginning of urine production by the mouse embryonic kidney around E16.5 and is well before the initial ureteral peristaltic waves that are first observed around E18.5 in mice.[35] It is still unclear when the ICC-LCs appear in human fetal ureter and at what embryonic stage human fetuses start to have rhythmic ureteral peristalsis.

Development of the bladder and urethra

Unlike the mesodermal ontogenetic origin of the kidney and ureter, the bladder and urethra arise from the endodermal urogenital sinus after the urorectal septum (i.e. Tourneux's fold) partitions the embryonic cloaca into the ventral urogenital sinus and the dorsal rectum.[39] At around 5 weeks of human gestation and at E11–12 in mouse, the urogenital sinus is further separated into the anterior vesicourethral canal and the posterior urogenital sinus. The anterior portion of the urogenital sinus (i.e. anterior vesicourethral canal) becomes the bladder, which has an open outflow tract at its apex that is connected to the allantois during early fetal life. This outflow tract is only functional at the early embryonic stage to drain the

developing bladder to the allantois through the umbilical cord. By ~15 weeks of human gestation, the bladder separates from the umbilicus as the allantois regresses and becomes a remnant called the urachus, which is further stretched to become the median umbilical ligament. In the meantime, the posterior vesicourethral canal becomes the pelvic portion of urethra in the male (which can be further divided into three segments: pre-prostatic, prostatic, and membranous urethra) and the entire urethra in the female. The posterior portion of the urogenital sinus later develops into the phallic urethra (also called spongy or penile urethra) in the male and the lower portion of the vagina and vaginal vestibule with perineal urethra orifice in the female.[39, 40]

By about four and half weeks of gestation in human and ~E12.5 in mouse, the common nephric duct (i.e. the posterior portion of the Wolffian duct distal to the ureteric budding site) shortens, expands and integrates into the urogenital sinus close to the region where the future bladder neck is located (Figure 1A, 1B).[41, 42] As the common nephric duct integrates into the bladder, it brings the ureteric budding site and anterior portion of the Wolffian duct with it.[41, 42] Recent studies have demonstrated that this is a vitamin-A dependent developmental process involving apoptosis of the common nephric duct, which eventually results in the transposition of the ureteric budding site from the Wolffian duct to the urogenital sinus epithelium to form the ureteral orifice.[43–45] The anterior portion of the Wolffian duct later becomes the vas deferens in males but regress in females. The openings of the vas deferens (Wolffian ducts) in males migrate gradually downward and medially and become the ejaculatory duct draining into the prostate portion of the urethra just below the bladder neck.[39]

After the integration of the common nephric ducts (CND) into the future bladder neck region in the urogenital sinus, the CND expands and moves the ureteric orifice anteriorly and separates it from the Wolffian duct. Subsequent developmental processes of CND apoptosis and expansion of the bladder body re-position the ureteric orifices in their final positions in the bladder wall.[45] Together with the internal urethral orifice, they form a triangular region at the base of the bladder that is also called trigone (Figure 1C). Although the trigone is traditionally considered as the only region in the bladder that is structurally different from the rest of the bladder and urethra[46], recent studies show that it is actually also derived from the endodermal bladder with only minor contribution from the mesodermal ureter.[47–49]

At the time that the early bladder is still part of the urogenital sinus, its lumen is lined by bilayered cuboidal and glycogen-rich epithelial cells surrounded by loose undifferentiated mesenchymal cells.[50] However, the developmental origin of these glycogen-rich epithelial cells is largely unknown. Similar to the kidney and ureter development, the epithelial-mesenchymal interaction is critical for proper bladder development.[51] At about 12 weeks of gestation in human and at E13.5 in mouse, bladder mesenchymal cells start to differentiate into smooth muscle cells.[50, 52] By 21 weeks of gestation, the human fetal bladder acquires three to five layers of urothelial cells similar to the fully differentiated urothelium, and a well-developed smooth muscle coat consisting of three layers of longitudinal and circular smooth muscles (also called detrusor).[50] In mouse, the urinary bladder becomes a fully developed organ after E15.5 with multi-layered urothelium expressing uroplakins and randomly oriented smooth muscle fibers that express α-smooth muscle actin.[52, 53]

The function of the human bladder is to store and empty urine. This requires normal bladder compliance for urine storage and urinary continence mechanism for emptying bladder in a coordinated and controlled manner. Bladder compliance increases during development as the thickness of the bladder muscle wall increases while the amount of collagen content decreases.[54, 55] A well developed human adult bladder normally can hold about 500 ml of

urine when it is full.[56, 57] However, we usually experience desire to micturate when the bladder contains only about 200–300 ml of urine. The molecular basis of bladder compliance formation and development is largely unknown.

The urinary continence mechanism is formed in a similar way in both male and female by a combination of muscles from the bladder detrusor, trigone, and urethral sphincter complex.[58] The urethral sphincter complex is derived from the sphincter urethrae primordium, an embryonic structure of mesenchymal condensation that can be identified in the urogenital sinus at nine weeks of gestation in human after the division of the cloaca.[59, 60] At about 13–15 weeks of gestation, the sphincter urethrae primordium starts to differentiate into two components of urethral sphincter complex that include the inner smooth muscle fibers (also called lissosphincter) and the outer striated muscle fibers (also called rhabdosphincter) (Figure 1C).[60] After 20 weeks of gestation, both lissosphincter and rhabdosphincter develop into an omega-shaped muscle coat surrounding the urethra with a narrow posterior connective tissue raphe that attaches to the lateral wall of the prostate in the male and the vagina in the female.[58–61] The smooth muscle lissosphincter also intermixes with the bladder detrusor and is abundant only in the proximal two thirds of the urethra below the bladder neck, whereas the striated muscle rhabdosphincter is predominantly located in the distal two thirds of the pelvic urethra.[60, 62] The urethral sphincter muscles are innervated by both autonomic nerves (pelvic plexus: regulates the proximal part of the urethra) and somatic nerves (pudendal nerves: control the contraction of the distal part of the urethra).[63–65] Normal development and innervation of both urethral sphincter muscles are likely to play a critical role in maintaining urinary continence after birth. The neural control of urinary continence has been thoroughly reviewed recently.[66]

As the bladder muscle mature, it also forms a muscle coat around the ureteric orifices in the trigone and functions as an “ureterovesical sphincter” that contracts in response to bladder contraction during voiding and subsequently relaxes following the closure of the external urethral sphincter complex during bladder filling.[67, 68] The contraction of the muscle coat around the ureteric orifices in the trigone acts as an “active” ostial-valve anti-reflux mechanism to prevent the retrograde urine flow from the bladder back to the ureter and kidney.[69–71] When the ureteric orifice establishes its final position in the bladder trigone, it guides the ureter to perforate the bladder muscle laterally in an oblique direction and proceed between the bladder mucosa and detrusor muscle to form an intravesical tunnel structure at the UVJ (Figure 1C). The intravesical portion of the ureter collapses during bladder voiding and creates a second anti-reflux mechanism also called the “passive” flap-valve mechanism.[72, 73] The active and passive anti-reflux mechanisms act together as a one-way valve allowing ejection of the bolus of urine from the ureter into bladder lumen when its pressure is low during bladder filling, and preventing retrograde flow of urine back to the ureter and kidney when the bladder pressure is high during micturition.[67, 68]

Genes and signaling pathways in lower urinary tract development and disease

Although only a few genes have been discovered so far associated with lower urinary tract birth defects in human, results from basic science research in the past 20 years provide us rich biological insights at the molecular level on early urinary tract development. Especially, many genes and signaling pathways have been identified to play important roles in early ureteric budding (Figure 2) and ureter development (Figure 3). Many common molecular signaling pathways important in other organ systems have also been shown to play significant roles in the development of the lower urinary tract. These include the receptor tyrosine kinase (RTK) signaling pathway (key known genes: *Gdnf, Ret*),[74] the Wnt signaling pathway (key known genes: *Ctnnb1, Wnt7b, Wnt9b, Fzd1*),[75] the Hedgehog signaling pathway (key known genes: *Shh. Gli3, Smo, Tshz3*),[31, 32, 76] the TGF-β signaling pathway (key known genes: *Bmp4, Smad4*),[77–79] the retinoic acid mediated nuclear receptor

signaling pathway (key known genes: *Rara, Rarb*),[44, 45, 80] and the renin-angiotensin system (key known genes: *Agt, Ren, Agtr1, Agtr2*).[81–85] (Figure 2 and 3; Table 1–4). Interestingly, not only are these signaling pathways required for the development of the lower urinary tract, but also the expression and activity of these genes and pathways are modified by lower urinary tract diseases. For example, recent global gene profiling studies have shown that UTI influences the activity of these signaling pathways.[86, 87] Throughout this review, we will refer to these molecular signaling pathways and link them to the phenotype of patients and/or mice with lower urinary tract diseases when these pathways are disrupted. Understanding the signaling pathways involved in lower urinary tract development and diseases can help us illuminate new directions for future genetic studies and identify novel candidate genes associated with these disorders in patients.

For the last 20 years, animal model studies have provided us an enormous amount of new knowledge regarding genes and signaling pathways involved in lower urinary tract development and congenital anomalies. The best animal model in the field is the mouse since lower model organisms have different developmental structures of the lower urinary tract compared to human. The high similarities between the human and mouse genomes together with mature genetic engineering technologies and large accessible mutant mouse resources provide excellent research tools to characterize the effects of human mutations in vivo.[88] The research tools in mouse genetics have evolved from positional cloning of spontaneous single gene mutations, ENU-mutagenesis screening, conventional gene knockouts, to spatially and temporally controlled induction of gene expressions and gene deletions in mice.[88, 89] The cell-specific deletions of genes in the lower urinary tract of mice using the Cre-lox system have revolutionized scientist's capacity to understand the role of major genes in urinary tract development, which often cause embryonic lethal phenotype in mice with germline mutations. For example, the mouse strain carrying the *Hoxb7-Cre* transgenic construct has enabled scientists to specifically knockout genes of interest in the epithelial cells of the ureteric bud lineage,[32, 90] while the *Tbx18-Cre* transgene enables researchers to specifically delete genes in the ureteral mesenchymal cells.[91] The Cre-lox system also enables scientists to perform fate mapping and cell lineage analysis in mice in order to understand the developmental origins of different cell types of the lower urinary tract system. These include cell lineage analysis of the epithelial cells of the Wolffian duct and ureteric bud,[92] the ureteral mensenchymal cells,[49, 78] the muscle cells of the bladder detrusor,[93, 94] and the distal urethra.[95]

GENETIC BASIS OF CONGENITAL ANOMALIES OF THE LOWER URINARY TRACT (CALUT)

Common congenital anomalies of the ureter

The major function of the ureter is to transport urine from the kidney to the bladder in a unidirectional manner. Therefore, congenital anomalies of the ureter and their associated junction structures (i.e. UPJ and UVJ) often cause abnormal urine transport including urinary obstruction (i.e. the blockage of urine transport from the kidney to the bladder that can be either physical or functional obstruction) and vesicoureteral reflux (VUR: retrograde flow of urine from the bladder back to the ureter and kidney). Both urinary obstruction and VUR elevate the pressure in the ureter and renal pelvis and can co-exist in the same patient.[96] Chronic and persistent urinary obstruction or VUR eventually cause dilatation of the renal pelvis (i.e. hydronephrosis) and dilatation of the ureter (i.e. hydroureter) (Figure 4A), which may facilitate colonization and grow of bacteria such as E. Coli in urine and predispose CALUT patients to recurrent UTI.[97]

The overall incidence of urinary obstruction and VUR in children is estimated at greater than 1% and is one of the most common problems encountered by pediatric nephrologists and urologists.[98–100] Patients with urinary obstruction and VUR at a young age may develop obstructive or reflux nephropathies featuring recurrent UTI, renal scarring, nephron loss, and compensatory hypertrophy of remnant nephrons.[101] Obstructive and reflux nephropathies ultimately cause proteinuria, degeneration of remnant nephrons, glomerulosclerosis, and tubular atrophy, which leads to chronic kidney insufficiency and end stage renal disease (ESRD).[102] It has been reported that about 10% of patients with reflux nephropathy will progress to chronic kidney insufficiency and ESRD, and eventually require dialysis or kidney transplantation.[103]

The pathogenesis of reflux nephropathy is not well understood, and it remains unclear why only a subset of patients progress to develop chronic kidney insufficiency and ESRD. The progression from reflux nephropathy to ESRD is almost always associated with proteinuria,[104] and most patients with reflux nephropathy and ESRD have focal segmental glomerulosclerosis (FSGS).[105] Over the past 30 years, the prevailing view about the pathogenesis of reflux nephropathy has been that high pressure from the refluxing urinary stream and recurrent UTI can result in renal injury and kidney parenchyma fibrosis or scarring also called “acquired” reflux nephropathy, which impairs kidney development and growth.[106–110] The pathogenesis of proteinuria and glomerulosclerosis in patients with “acquired” reflux nephropathy and progressive renal insufficiency remains controversial. At least four mechanisms have been proposed, which include immunologic injury, macromolecular trapping and mesangial dysfunction, vascular alterations, and glomerular hypertension.[111] On the other hand, the clinical course resulting in reflux nephropathy and ESRD does not appear to be altered by either surgical correction of VUR or control of UTI and hypertension.[104, 112–114] Many scientists and clinicians believe that many VUR children with urinary tract congenital abnormalities actually develop congenital renal scar before birth.[115] These patients will progress to “congenital” reflux nephropathy and renal insufficiency due to abnormal ureteral and kidney development even in the absence of UTI and associated inflammatory reaction in the kidney.[116]

Genetic basis of vesicoureteral reflux (VUR)

VUR can be caused by a variety of birth defects affecting the lower urinary tract development. These include defects in ureteric budding, ureter differentiation and elongation, peristalsis, UVJ formation, and bladder and urethra development. In patients with primary VUR, the location of the ureteric orifice (i.e. UVJ) of a ureter tends to be located laterally and more cephalad in the bladder.[41, 117] This results in a shortening of the submucosal ureteric segment and a weakening of the flap-valve anti-reflux mechanism and VUR ensues. The degree of reflux may correlate with the degree of ureteric orifice laterality and inversely with the length of the intravesical submucosal ureter.[118] The lateral ectopia of the ureteric orifice may be related to abnormal development of the embryonic ureteric bud (Figure 4B–4D), which is also called Machie and Stephens hypothesis or “bud theory”.[41]

The “bud theory” developed by Machie and Stephens proposes that the ureteral orifice derives from the original ureteric budding site on the Wolffian duct during embryonic development (Figure 1A). When the ureteric buds arise at abnormal sites of the Wolffian duct, such as multiple ureteric buds (Figure 4B), the final sites of the ureteral orifices may also be abnormal (Figure 4C, 4D), resulting in defective ureterovesical junctions, VUR or UVJ obstruction. Machie and Stephens suggest that the final sites of the ureteral orifices in the bladder are determined by the insertion of the common nephric duct into the bladder and its expansion to form the trigone. However, recent cell lineage studies show that the common nephric duct does not differentiate into the trigone but instead undergoes apoptosis.[44] Subsequent expansion of the bladder repositions the ureteral orifices to their

final positions in the bladder trigone.[44, 45] In addition, multiple ureteric buds may also lead to short duplex ureters, duplex kidneys, ectopic and dysplastic kidneys (Figure 4A, 4C, 4D).[10, 41, 44, 45, 77, 119–122] Therefore, mutations of genes controlling early ureteric buds formation and positioning often cause ureteral phenotypes such like urinary obstruction, VUR and hydronephrosis during fetal life and after birth in both human and mouse (Figure 2, Table 1–2).[25, 42, 122–124]

Many syndromes have VUR as one of the phenotypes. These include Sotos, Cornelia de Lange, Diamon Blackfan, Duane Radial ray, Langer-Giedion, Kallmann, EEC1 syndrome, etc. (Table 1). Although for some of them the underlying genes have been identified, the genetic basis of primary nonsyndromic VUR remains ill-defined.[125] Family studies show familial clustering of reflux and imply a genetic origin for primary VUR. About 45–50% percent of children with primary VUR are from families where at least one additional family member is affected.[126, 127] The disease often occurs in two or more generations with up to a 65% transmission rate from parents to children,[128, 129] and 34–45% of an affected patient's siblings will have reflux.[130–132] One study has showed that 80% of identical twins and 35% of fraternal twins develop primary VUR.[126] These data strongly support a genetic basis for primary VUR and are consistent with an autosomal dominant mode of inheritance, albeit with incomplete penetrance.[133]

Segregation analysis has concluded that primary VUR is caused by a major dominantly inherited allele.[134] Mutations in *PAX2* on chromosome 10q cause the coloboma-ureteric-renal syndrome (also called Papillorenal syndrome, OMIM 120330), in which VUR is part of the phenotype.[7, 135] Recently, mutations in several other genes have also been identified associated with primary VUR.[136] These include *ROBO2* (VUR2, OMIM 610878),[10, 136, 137] *SOX17* (VUR3, OMIM 613674),[138], *UPK3A*[139], and *RET*[140, 141] (Table 1). However, all these VUR genes have been excluded as major players in primary nonsyndromic VUR.[136, 142–147]

Human *ROBO2* mutations have been identified in patients with VUR from several unrelated families.[10, 137] *Robo2* is a member of the immunoglobulin superfamily and encodes a cell adhesion molecule involved in axonal guidance and neurogenesis.[148, 149] It is a receptor for the Slit2 ligand,[150] and Slit2-Robo2 signaling acts as a chemorepulsive guidance cue to control axon pathfinding and neuron migration during nervous system development.[151] Slit2-Robo2 signaling also plays crucial roles in early ureteric buds outgrowth and positioning. Mouse knockouts that lack either *Slit2* or *Robo2* develop supernumerary ureteric buds, duplex kidney and hydroureter phenotype.[10, 119] A recent study further demonstrates that *Robo2* is critical for the formation of normal ureteral orifices and for the maintenance of both active and passive anti-reflux mechanisms.[123] Interestingly, Robo2 signaling has also recently been shown to act as a negative regulator on nephrin to influence podocyte foot process architecture in kidney glomeruli.[152]

Mutations in genes controlling early ureteric buds formation

Gdnf is the most important inducer of UB outgrowth through the receptor tyrosine kinase (RTK) signaling pathway and is mediated by its receptor Ret (Figure 2).[17, 74] The *Gdnf* gene encodes a highly conserved secreted protein in the metanephric mesenchyme and induces ureteric buds outgrowth during early kidney and ureter development.[17, 74] Loss of *Gdnf* in mice causes absence of ureteric buds formation and renal agenesis.[153] Therefore, mutations in genes associated with the Gdnf/Ret pathway, like *Spry1, Gata3, Bmp4, Slit2/Robo2, Foxc1/2, Pax2, Eya1/Six1*, and *Sall1*, all cause abnormal ureteric budding phenotypes in mice (Figure 2, Table 1–2).[10, 77, 119–121, 154–158]

The *Ret* gene encodes a receptor tyrosine kinase in the UB and interacts with its ligand Gdnf secreted from MM (Figure 2). Mutations in *RET* have been identified in patients with VUR, ureteral obstruction, megaureter, duplex kidney, renal abnormalities, as well as Hirschsprung's disease and cancer.[141, 159–161] Yang and colleagues have observed a significant association between primary VUR and a G691S polymorphism (rs1799939) in the *RET* gene among French Canadian VUR patients.[140] In mice, *Ret* mutations cause similar defects as in humans, which include renal agenesis, hypoplasia, ectopic ureter termination, and enteric nervous system defects.[162–165] Interestingly, a study shows that overexpression of *Ret* in mice also causes VUR phenotype.[166] *Spry1* is a negative regulator of RTK signaling and acts as a negative feedback to balance the Gdnf/Ret signaling in the UB. In mice, mutations in *Spry1* cause multiple ureteric buds and hydroureter.[120] Accordingly, loss of *Spry1* is able to rescue mouse *Gdnf* and *Ret* knockout phenotypes.[167, 168] However, no *SPRY1* mutations have been identified so far in human VUR or other lower urinary tract birth defects.[169]

Mutations in *GATA3* in human have been identified as a cause of Hypoparathyroidism, sensorineural Deafness, and Renal disease (HDR: OMIM 146255), which includes renal dysplasia, unilateral kidney agenesis and VUR phenotypes.[170, 171] In mice, loss of *Gata3* leads to ectopic ureteric budding, duplex kidney, hydroureter, as well as vas deferens hyperplasia and uterine agenesis.[154] *Gata3* is a transcription factor of the GATA family that is expressed in the ureteric buds.[172] It is regulated by the *Pax2* and *Pax8* genes and is a key regulator of the Wolffian duct morphogenesis.[173] Molecular analysis has further placed *Gata3* upstream of *Ret* but downstream of β-catenin, preventing ectopic ureter budding and premature cell differentiation in the Wolffian duct (Figure 2).[154]

The Axenfeld-Rieger syndrome (OMIM 602482) is caused by mutations in *FOXC1*, a transcription factor of the forkhead family that is highly expressed in the metanephric mesenchyme. Recently, Weisschuh and collaborators have described a ureteral stenosis phenotype in patients with Axenfeld-Rieger syndrome.[174] Interestingly, in mouse, mutations in *Foxc1* and its family member *Foxc2* result in the expansion of the *Gdnf* expression domain in the metanephric mesenchyme, which leads to a urinary tract phenotype including ectopic ureteric buds, duplex ureters, and hydroureters.[121] In addition, mutations in the transcription factor *FOXF1*, another family member of the forkhead box genes, cause the “Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins” syndrome (ACDMPV: OMIM 265380). ACDMPV is associated with ureteral valve-like constriction at the UPJ, tortuous ureters, and hydronephrosis.[174, 175] *FOXF1* is located at the same chromosomal locus as *FOXC2*, and is a part of the sonic hedgehog and TGF-β signaling pathways.[176] Other genes in the sonic hedgehog and TGF-β signaling pathways also play critical roles in lower urinary tract development and congenital anomalies (Figure 3). *FOXF1* is the only gene so far that has been associated with UPJ obstruction in human.

In mice, mutations in several genes have been shown to cause UPJ obstruction and ureter-bladder connection defects.[43, 44, 177, 178] For example, loss of both retinoic acid receptor alpha (*Rara*) and beta (*Rarb*) in mice lead to megaureter and hydronephrosis owing to abnormal apoptosis activity mediated by vitamin A signaling at the ureter-bladder insertion site.[43, 44] In mice with double knockout of the genes encoding the protein tyrosine phosphatase receptor type F and S (*Ptprf* and *Prpts*), the regression of the common nephric duct is delayed resulting in inappropriate tissue survival and delayed distal ureter maturation. These ureter-bladder connection defects cause urinary obstruction, hydroureter and hydronephrosis in *Ptprf;Prpts* double mutant embryos.[178] A recent study also shows that the Gata3-Raldh2-Ret molecular network plays a crucial role in regulating the proper insertion of the nephric duct into the mouse developing bladder.[177] Absence of *Ret*, *Gata3*,

or *Raldh2* can cause similar distal ureter insertion defects with urinary obstruction and hydronephrosis phenotypes in mice.[177]

Interestingly, despite the common ontogenetic origin of the kidney and the ureter, some transcription factors in the early metanephric mesenchyme enabling the ureteric buds outgrowth may induce the ureter formation but not the kidney. For example, mutations in *SALL1*, a transcriptional factor expressed in the MM that enhances the canonical Wnt signaling pathway, is responsible for the Townes-Brocks Syndrome (TBS: OMIM 107480).[179] Homozygous deletion of *Sall1* in mice results in apoptosis of the mesenchyme and renal agenesis but normal blind-ended ureter. This phenotype can be rescued by lowering beta-catenin levels in the *Sall1* mutant.[157] Heterozygous *SIX1* mutations are known to cause the Branchiootic Syndrome 3 (BOS3: OMIM 608389). However, mice homozygotes for *Six1* mutations develop ureters in the absence of kidneys[180], but the ureteral mesenchymal precursors fail to condense and differentiate into normal smooth muscle in the ureters.[155] Interestingly, loss of the *Eya1* gene (the transcriptional activator interacting with Six1 in the MM) causes agenesis of both the ureters and kidneys due to a failure of the ureteric buds outgrowth and metanephric induction[156]. Mutations in *EYA1* in humans cause Branchio-oto-renal Syndrome (BOR: OMIM 113650) which is characterized by renal tract abnormalities ranging from mild renal hypoplasia to a complete absence of the kidney, as well as duplex ureters, VUR and ureteropelvic junction stenosis.[181]

Mutations in genes controlling ureter development

Ureter developmental malformations often lead to hydronephrosis (excessive water inside the renal pelvis and calyces). Antenatal hydronephrosis (ANH) is one of the most common congenital abnormalities detected with prenatal ultrasonography in more than 1% of all pregnancies.[182, 183] ANH can be caused by a wide spectrum of renal and urological conditions ranging from transient hydronephrosis that resolves spontaneously after birth to clinically significant VUR or urinary tract obstruction that leads to renal failure.[184, 185] Because the advancement of latest medical technologies has not provided a gold standard for the diagnosis of clinically significant hydronephrosis, the evaluation and treatment of ANH is an area of considerable controversy among medical professionals.[186] Much of the controversy that surrounds the diagnosis and management of ANH stems from a lack of understanding of the molecular etiologies and developmental origins of this common birth defect.

Recent genetic studies in both human and mice have identified many genes associated with hydronephrosis due to lower urinary tract abnormalities (Table 2). Antenatal hydronephrosis can originate from kidney defects (e.g. mutations in *AQP2* gene that encodes aquaporin 2 water channel in the kidney collecting tubule[187]), or from defects in the ureter such as VUR or urinary obstruction.[186, 188] Mutations in many genes controlling the developmental processes of different components of the ureter have been shown to cause hydronephrosis in mice (Figure 3). For example, deletions of uroplakins (*Upk3a* and *Upk2*) in the urothelium in mice cause loss of superficial umbrella cell layer, overgrowth of the urothelium, urothelial leakage, which lead to hydronephrosis and VUR.[27, 28] In addition, mutations in *UPK3A* have been found in patients with dysplastic kidney, hydronephrosis and VUR.[139] Stromal cells (marked by *Raldh2* expression) are also important for normal ureteral development and function.[189, 190] Loss of Discs-large homolog 1 (*Dlg1*) has been shown to cause absence of the stromal cell layer in the ureter, which leads to abnormal ureteral smooth muscle orientation, impaired ureteral peristalsis, and severe antenatal hydronephrosis.[189, 190] *Dlg1* is the only gene identified so far that is required for ureteral stromal cell formation.

Many genes associated with hydronephrosis in mice are genes controlling ureteral typical smooth muscle cell development (Figure 3). These include genes in the sonic hedgehog

pathway (e.g. *Shh, Gli3, Smo, Tshz3*),[31, 32, 76] the TGF-β pathway (e.g. *Bmp4, Smad4*),[77–79] and the Wnt pathway (e.g. *Ctnnb1*).[75] A recent study from Trowe and colleagues also shows that canonical Wnt signaling is required for the ureteral adventitial fibroblast differentiation.[75] In mice, loss of the T-box transcription factor *Tbx18* causes a failure of the ureteral mesenchymal cells to differentiate into ureteral smooth muscle cells as well as an abnormal differentiation of the urothelium, leading to UVJ obstruction, short hydroureter, and antenatal hydronephrosis.[29] The abnormal smooth muscle phenotype in *Tbx18* mutant mice might be caused by the downregulation of the sonic hedgehog signaling (e.g. *Ptch1*) in the ureteral mesenchyme and *Bmp4* expression in the ureter.[29, 191] Taken together, these results underscore the importance of normal development of the typical smooth muscle cells in the ureter, which produce contractile forces to propel urine from the kidney to the bladder.[192]

Several recent studies also demonstrate the importance of genes controlling ureteral pacemaker cell development and peristalsis machinery in the pathogenesis of hydronephrosis.[35, 76, 193, 194] In the urinary tract, the proto-oncogene *Kit* marks interstitial cells of Cajal (ICC) – like cells (ICC-LCs).[35] Recently, *Hcn3* (hyperpolarization-activated cation channel 3) has also been identified as playing a fundamental role to trigger and coordinate proximal-to-distal ureter peristalsis.[194] In mice, inactivation of *Smo* (Smoothened) and upregulation of the *Gli3* repressor, two components of the sonic hedgehog signaling pathway, lead to abnormal ureteral peristalsis, nonobstructive hydronephrosis and hydroureter before birth.[76] Although the urothelium and smooth muscle cells develop normally in these mutant mice, the number of ureteral pacemaker cells (marked by *Kit* and *Hcn3* expression) in the renal pelvis and the ureter are significantly reduced.[76] This study provides a strong evidence that sonic hedgehog signaling controls ureteral pacemaker cell development and defective pacemaker cell differentiation can lead to abnormal ureteral peristalsis and hydronephrosis.[76, 195] Consistent with this finding, mutations in *GLI3* gene have been identified in patients with the Pallister-Hall syndrome (PHS, OMIM: 146510), which includes urinary tract phenotypes like hydronephrosis and hydroureter.[196–198]

In another study, Chang and colleagues have shown that expression of one of the calcineurin subunit B isoform gene *Cnb1* (also called *Ppp3r1*) is required in the mouse urinary tract mesenchyme for the development of the pyeloureteral peristaltic machinery.[193] Tissue specific knockout of *Cnb1* in mice cause an abnormal formation of the renal pelvis and ureter as well as defective pyeloureteral peristaltic waves, which lead to progressive renal tract obstruction and hydronephrosis after birth.[193] The angiotensin type 1 receptor (*Agtr1*) has also been shown to play a role in ureteral peristalsis since *Agtr1* knockout mice have abnormal renal pelvis and lack ureteral peristaltic waves, and subsequently develop hydronephrosis phenotype.[199] However, no causal mutations in either *CNB1* or *AGTR1* have been reported in patients with lower urinary tract anomalies although mutations in *AGTR1* are associated with autosomal recessive renal tubular dysgenesis (RTD).[81, 200]

Genetic basis of congenital anomalies of the bladder

Compared with known causative genes identified in kidney anomalies and hydronephrosis, the knowledge of the genetic basis for bladder congenital anomalies is very limited (Table 3). Congenital anomalies of the bladder range from severe life-threatening birth defects like bladder agenesis, megacystis, bladder-exstrophy-epispadias complex (BEEC), prune belly syndrome (PBS) to relative mild dysfunctions of the bladder muscle, bladder diverticula, and dysfunctional urinary voiding.[201] These birth defects of the bladder can have a significant deleterious effect on the kidney function in children.[202] Bladder agenesis is extremely rare and often associated with urethral agenesis as well as other urinary anomalies including hydronephrosis, duplex kidney, and ectopic ureter draining into the vagina, uterus

or rectum.[203] The genetic basis of bladder agenesis is unknown. The vast majority of patients reported are female infants although two viable male infants have also been reported.[204]

Megacystis (abnormally large or distended bladder) are often associated with chromosome abnormalities such as trisomy 13 and trisomy 18.[205] It can also manifest as one of the phenotypes in male fetuses with lower urinary tract obstruction as a consequence of urethral obstructive congenital anomalies such as posterior urethral valves (PUVs) or urethral atresia.[206] In female fetuses, megacystis can be caused by cloacal plate anomalies such as megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIH, OMIM: 249210), which is a rare genetic disease with autosomal recessive inheritance.[207, 208] The causal gene for MMIH has not been identified. A unique transgenic mouse model called *mgb* develops megabladder, hydronephrosis, obstructive uropathy, and renal failure. The homozygous *mgb* mice nearly completely lack the bladder detrusor muscle and develop prenatal megacystis with altered bladder smooth muscle development.[209, 210] The megabladder phenotype in *mgb* mouse is believed to be caused by the disruption of an endogenous gene due to a random insertion of a transgene construct into a region of mouse chromosome 16 that then translocates to chromosome 11.[209] So far, the cloning of the endogenous causal gene disrupted by the transgene insertion or the chromosome translocation in *mgb* mouse has not been reported.

The bladder-exstrophy-epispadias complex (BEEC) represents a spectrum of congenital anomalies characterized by defects with different severities in the closure of the lower abdominal wall and the bladder.[211] Depending on the severity, BEEC can be subdivided into Epispadias (E: the mildest form), Classical Bladder Exstrophy (CBE: intermediate severity), and Cloacal Exstrophy (CE: the most severe form).[211, 212] Epispadias and bladder exstrophy occur more often in males while the majority of patients with cloacal exstrophy are females. Epispadias is characterized by an open male urethral plate or a cleft in the female's urethra.[212] Patients with bladder exstrophy have the bladder and related structure (e.g. bladder mucosa, trigone, bladder neck and urethra) everted through the ventral wall of the abdomen and is visible from the outside between the umbilicus and symphysis pubis.[213] In cloacal exstrophy, in addition to bladder exstrophy, most patients also have omphalocele (intestine or other abdominal organs protrude into the navel) and imperforate anus, while others have spine defects and renal malformations (also called OEIS complex – Omphalocele, bladder Exstrophy, Imperforate anus, Spine defects).[214] The etiology of BEEC has not been resolved. Studies suggest that genetic factors may play a role and several familial BEEC cases have been reported.[211] Although BEEC can occur as a part of syndromes, most of the reported cases are isolated.[211, 215] Cytogenetic and array-CGH analyses have revealed several BEEC cases with chromosomal abnormalities including a de novo reciprocal chromosomal translocation between 8p11.2 and 9q13 disrupting *CNTNAP3* gene that encodes a cell adhesion and recognition molecule of the NCP (Neurexin-IV/Caspr/Paranodin) family.[216] Recently, a chromosomal microduplication at 22q11.2 has also been identified in three bladder exstrophy patients by two research groups using array-CGH and genome-wide SNP arrays.[217, 218] However, no causal relationship of any single gene mutations and BEEC has been established in human so far. A mouse model with *Tp63* (a transcription factor of *p53* tumor protein family) deletion has recently been shown to have bladder exstrophy and absence of abdominal and ventral bladder walls with increased apoptosis in the ventral bladder urothelium.[219] However, no *TP63* mutations have been reported in human BEEC cases.

Prune belly syndrome (PBS) is a rare lower urinary tract birth defect affecting about 1 in 30,000 births.[220] PBS is characterized by three major defects that include a partial or complete lack of abdominal muscle with a dry prune like wrinkly skin appearance of the

abdomen (so-called prune belly), urinary tract dilatation such as distended thin-walled bladder with disorganized detrusor muscle, bilateral hydroureter and hydronephrosis, and cryptorchidism.[221] The majority of PBS patients are males and often have coexisting morbidities such as pulmonary hypoplasia, VUR, urethra abnormalities, chronic pyelonephritis and dysplastic kidney, which commonly lead to renal failure and kidney transplantation.[221, 222] Several cases of familial PBS have been reported with an autosomal recessive mode of inheritance.[223] A deletion of *HNF1B* (hepatocyte nuclear factor 1B) has also been reported in a few PBS cases.[224, 225] Although mutations in *HNF1B* are known causes for renal cysts and diabetes syndrome[226], familial glomerulocystic kidney disease,[227] and renal hypodysplasia.[228], it is still unclear if *HNF1B* is one of the causative genes for PBS.[229] Recently, a homozygous nonsense mutation of *CHRM3* (muscarinic cholinergic receptor 3) has been identified in six male patients from one family with congenital bladder malformation associated with a prune-belly-like syndrome.[230] *CHRM3* is expressed in human and mouse bladder urothelial and detrusor muscle cells.[230] In mice, *Chrm3* has been shown to play a key role in bladder detrusor contractions and *Chrm3* knockout mice develop distended bladder with thin bladder smooth muscle layer that resembles the bladder phenotype in PBS patients.[231] It would be interesting to see whether *CHRM3* mutations will be identified in other PBS cases.

Congenital bladder diverticulum is characterized by a bladder mucosa herniation through muscular fibers of the bladder wall. It often occurs in the region of the bladder where the detrusor muscle is thin due to abnormal bladder development.[232, 233] The majority of congenital bladder diverticula are located close to the ureteral orifice (so-called paraureteral diverticula), which can disrupt the anti-reflux mechanism and lead to VUR, UTI, and hydronephrosis.[234] About 10% of congenital bladder diverticula occur in the posterolateral region of the bladder, which can grow very large and cause bladder outlet obstruction.[235] The genetic basis of congenital bladder diverticula is unclear. Since the diverticula are often associated with incompetent ureteral orifices, it could be caused by mutations in genes controlling early ureteric budding and UVJ formation.[232] Bladder diverticula can also occur as part of a number of congenital syndromes, such as occipital horn syndrome (OMIM: 304150, can be phenotypically overlap with Menkes disease – OMIM: 309400),[236, 237] Williams-Beuren syndrome (OMIM: 194050),[238–240] Ehlers-Danlos syndrome (OMIM: 130000),[241, 242] and cutis laxa syndrome with severe pulmonary, gastrointestinal, and urinary abnormalities (OMIM: 613177)[243] (Table 3).

The urofacial syndrome (USF, OMIM: 236730, also called Ochoa syndrome) is a rare autosomal recessive disorder characterized by a severe and early-onset urinary voiding dysfunction, bowel dysfunction, and a unique inverted facial grimacing expression when patients attempt to smile.[244] USF patients often have neurogenic bladder like symptoms such as urinary incontinence, bladder-sphincter dysfunction, UTI, constipation or encopresis, but without apparent neurological or obstructive pathology. If USF is not diagnosed and treated early, the disease often impairs urine flow causing severe VUR, recurrent UTI, kidney damage, hypertension, and renal failure.[244–246] Recently, mutations in the *HPSE2* gene have been identified as causing USF. Both microdeletion and nonsense point mutations in *HPSE2* have been identified in multiple unrelated familial USF cases by different research groups.[247–249] *HPSE2* encodes Heparanase 2 which is an endoglycosidase that degrades heparin sulfate proteoglycans and is located on the extracellular matrix and cell surface.[250] *HPSE2* is highly expressed in human and mouse tissues of the bladder, ureter, kidney and brain.[248] However, it is unclear how absence of *HPSE2* expression in the urinary tract and brain tissues causes USF phenotype in human. There is no *Hpse2* mutant animal model currently available for further mechanistic study.

Genetic basis of congenital anomalies of the urethra

The anatomical structures of the urethra are different between males and females. Because additional developmental processes are involved in the formation of male phallic urethra, congenital anomalies of the urethra occur more often in male infants, and include hypospadias, posterior urethral valve (PUV), and anterior urethra abnormalities. Female infants can develop congenital anomalies of the urethra as well, and they are often more severe than males and are associated with congenital defects of the bladder, the vagina, or the rectum. For example, epispadias, which is part of bladder-exstrophy-epispadias complex (BEEC) described previously, can occur in female children.[251] Persistent cloaca, one of the most severe types of anorectal malformation with defects in the urethra, the vagina, and the rectum, is seen exclusively in girls.[252–254] It is characterized by a single common channel in the perineum for the drainage of the urethra, the vagina, and the rectum, owing to the failure of proper cloaca separation in early embryonic development.[252] Persistent cloaca is often associated with other urinary tract abnormalities including VUR, hydroureter, hydronephrosis, UPJ obstruction, renal dysplasia, which all may lead to chronic kidney insufficiency and renal failure.[255] Persistent cloaca can be detected prenatally,[256] however, the genetic basis of this congenital anomaly is presently unknown. In mice, deletion of either or both *Eya1* and *Six1* genes has recently been shown to cause persistent cloaca,[257] although it has not been reported in patients with branchio-oto-renal syndrome (caused by mutations in *Eya1* or *Six1*).

Hypospadias is one of the most frequent urogenital birth defects in male newborns with an incidence ranging from 1/1000 to 1/100 births.[258, 259] It is defined as a midline fusion defect of the male urethra and penis that results in an ectopic opening of the urethral meatus along the ventral region of the male urethra.[260] The causes of hypospadias are considered multifactorial, involving both genetic and environmental factors and have been extensively reviewed recently.[261–263] Intensive investigations in the past 20 years have identified many genes that are associated with hypospadias (Table 4). Single gene mutations have been found in *WT1, SF1, BMP4, BMP7, FGF8, FGFR2, AR, HSD3B2, SRD5A2, ATF3, MAMLD1, MID1* and *BNC2*.[263] In addition, hypospadias has been associated with polymorphisms in many other genes including *FGF8, FGFR2, AR, HSD17B3, SRD5A2, ESR1, ESR2, ATF3, MAMLD1, DGKK, MID1, CYP1A1, GSTM1* and *GSTT1*.[263] Studies of gene expression in patients with hypospadias further identify *CTGF, CYR61* and *EGF* as potential new candidate genes.[263] Hypospadias can also be part of syndromes like the Hand-Foot-Genital syndrome (OMIM: 140000), which is caused by mutations in *HOXA13*.[264] The environment risk factors for hypospadias may include low birth weight, maternal hypertension, pre-eclampsia, and maternal exposure of exogenous endocrine-disrupting chemicals.[263] However, the majority of isolated hypospadias cases remain unexplained and the major genetic or environmental risk factors for hypospadias are still elusive.

Posterior urethral valve (PUV) is the most common cause of lower urinary tract obstruction in male infants. It is characterized by the formation of sail-like membrane folds from the verumontanum in the posterior urethra at early embryonic stage, which causes obstruction of urine flow and persistent high pressure in the bladder, the ureter and the kidney throughout development.[265, 266] PUV is often diagnosed in fetuses with antenatal hydronephrosis during ultrasound examination and is associated with megacystis, thickened bladder wall, and posterior urethra dilatation (observed collectively as a keyhole sign in the bladder neck by ultrasound). If PUV is not corrected early with urethral catheter and cystoscopic valve ablation, it can cause severe VUR, reflux nephropathy, chronic kidney disease and renal failure.[267, 268] The fetal origin of PUV formation is still ill-defined. It is thought to occur due to an abnormal insertion of the Wolffian duct into the cloaca during early development resulting in the formation of abnormal ridges or folds in the posterior urethra.[266] So far, no causative genes have been identified for PUV although familial inheritance of this birth

defect has been reported.[269] Recently, a genetic association has been reported between renal damage in PUV and polymorphisms of two renin-angiotensin system genes, *ACE* (angiotensin converting enzyme and *AGTR2* (angiotensin II receptor type 2).[270] Urethral valve can also occur in the anterior region of the urethra (so-called anterior urethral valve).[271, 272] Together with urethral diverticulum and megalourethra, they constitute a group of rare congenital anomalies of the anterior urethra.[273–275] Overall the renal outcome and prognosis of congenital anomalies of the anterior urethra are generally good. The genetic basis of these urethral birth defects is currently unknown.[276, 277]

CONCLUSION AND FUTURE DIRECTIONS

Congenital anomalies of the lower urinary tract account for 20–30% of all anomalies identified in the prenatal period. During pregnancy, routine prenatal ultrasound examination enables early detection of many lower urinary tract anomalies in fetuses (e.g. antenatal hydronephrosis) prior to the development of renal tract complications such as UTI, kidney stones and renal insufficiency.[186] Although some lower urinary tract phenotypes (such as antenatal hydronephrosis) will resolve spontaneously in many fetuses after birth, the prenatal detection of hydronephrosis during pregnancy brings a heavy psychological burden on the parents. When an anomaly is detected during obstetric ultrasound scan, a decision regarding the pregnancy is strongly influenced by the definitive diagnosis and prognosis of the condition.[278] Since a long list of genetic syndromes and chromosomal abnormalities is associated with hydronephrosis (Figure 5), the decision regarding a pregnancy and fetal intervention with antenatal hydronephrosis can be difficult. Especially, only few causative genes have been identified so far in patients with isolated or non-syndromic lower urinary tract birth defects that may lead to progressive renal injury and chronic kidney disease after birth. Therefore, it is important to identify new causative genes for lower urinary tract birth defects and related signaling pathways and biological processes that may affect renal outcome and prognosis.

In the field of human genetics, tests using DNA microarrays were developed in the late 1990s and introduced into the clinic at the beginning of this century. This genomic approach enables clinicians and scientists to uncover chromosome microdeletions and microduplications and to identify genomic loci associated with a range of human diseases. In the past few years, exome and whole genome sequencing have been developed and introduced in human genetic research and clinical diagnosis. These new genetic and genomic diagnostic technologies have revolutionized the field of personalized medicine as well as genetic counseling in both prenatal and postnatal care settings. However, the large amounts of genetic and genomic data that are gathered from these diagnostic tests are very difficult to interpret even by medical professionals. Many copy number variations (CNVs) and single nucleotide polymorphisms (SNPs) have been discovered in patients as well as healthy controls. The causality of these variants is hard to prove with the tools of human genetics alone.

The knowledge derived from patients and model organisms such as mice is complementary since human genetics can identify candidate genes associated with lower urinary tract birth defects, while mouse models can provide additional validation for that causal association and further uncover the disease mechanism at the molecular level. Knowledge gained by comprehending the molecular mechanism can also lead to new candidate genes. As data on gene expression and mutant strains of the laboratory mice are increasingly available to the scientific community, now is the most exciting time to perform high-throughput mouse model phenotype analysis to verify candidate genes for human lower urinary tract birth defects[279–282]. Knowledge deduced from these studies may have long term implications on preventive interventions aimed at reducing the incidence of lower urinary tract birth defects

and minimize further renal injury caused by CALUT (e.g. progressive hydronephrosis or high-grade VUR) and preserve remaining renal function. Understanding the signaling pathways involved in the lower urinary tract development and function may also fill an important scientific knowledge gap at the junction of basic science research and clinical implications, which would lead to new opportunities for prenatal screening, diagnosis and therapy.

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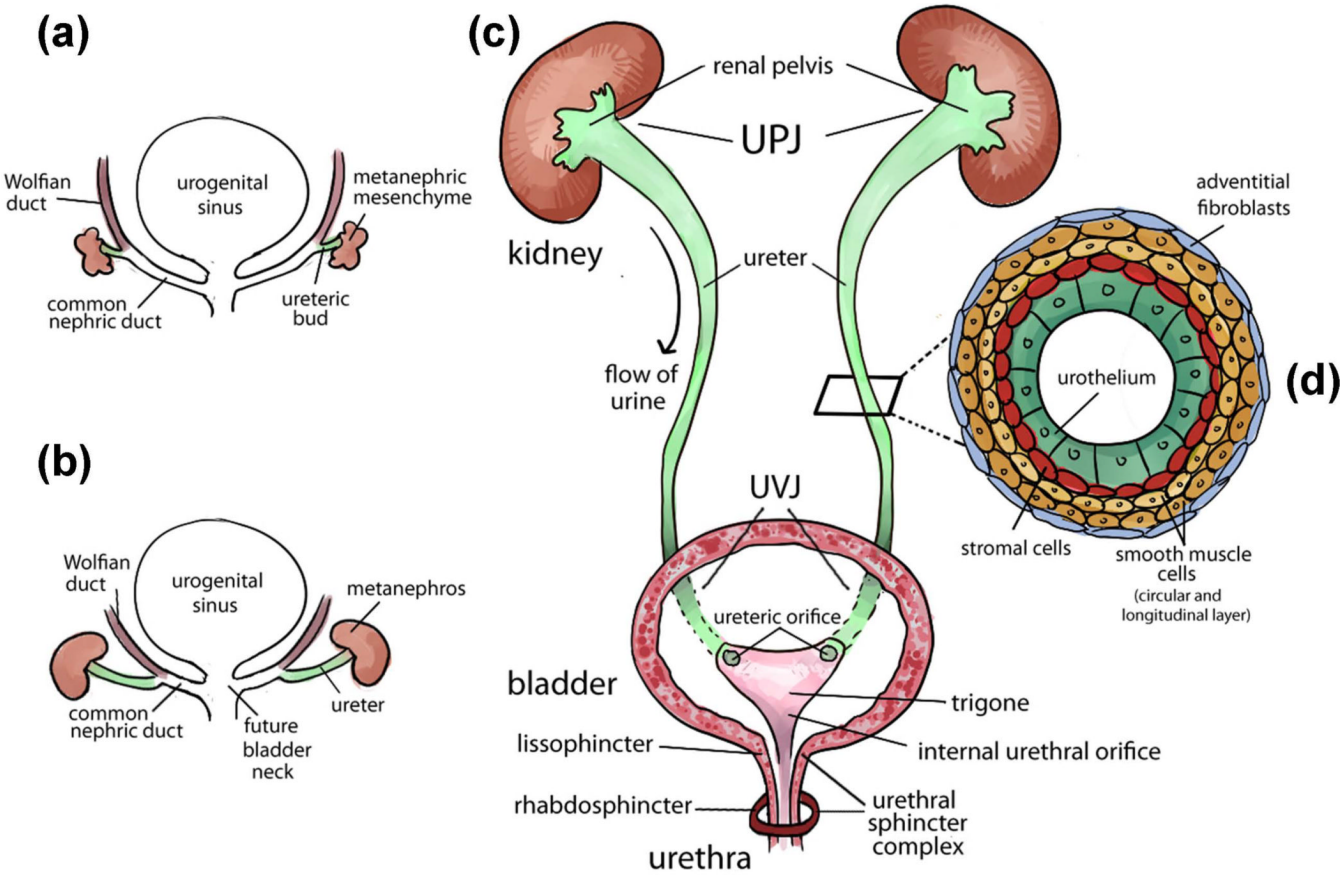

FIGURE 1.

Urinary tract development and structure. (a) Early development of the urinary tract (4th week of gestation in human and E10.5 in mice). An epithelial diverticulum called ureteric bud (UB) emanates from the Wolffian duct and grows into an adjacent group of mesenchymal cells (metanephric mesenchyme). (b) Elongation of the ureter and formation of the kidney (metanephros) during development. The common nephric ducts shorten, expand and integrate into the urogenital sinus (the future bladder) close to the region where the future bladder neck is located. (c) Structure of mature urinary tract in human and mice. Urine flows from the renal pelvis in the kidney through the ureter to the bladder for storage and eliminates to the outside through the urethra. The ureter is connected to the kidney at the ureteropelvic junction (UPJ) and is connected to the bladder at the ureterovesical junction (UVJ). Inside the bladder, two ureteric orifices and the internal urethral orifice form the trigone. The urethral sphincter complex includes the lissosphincter which is a continuation of the bladder smooth muscle and the rhabdosphincter which consists of striated muscles. (d) Transverse section of the mature ureter depicts four layers of cells: urothelium, stromal cells, smooth muscle cells and adventitial fibroblasts.

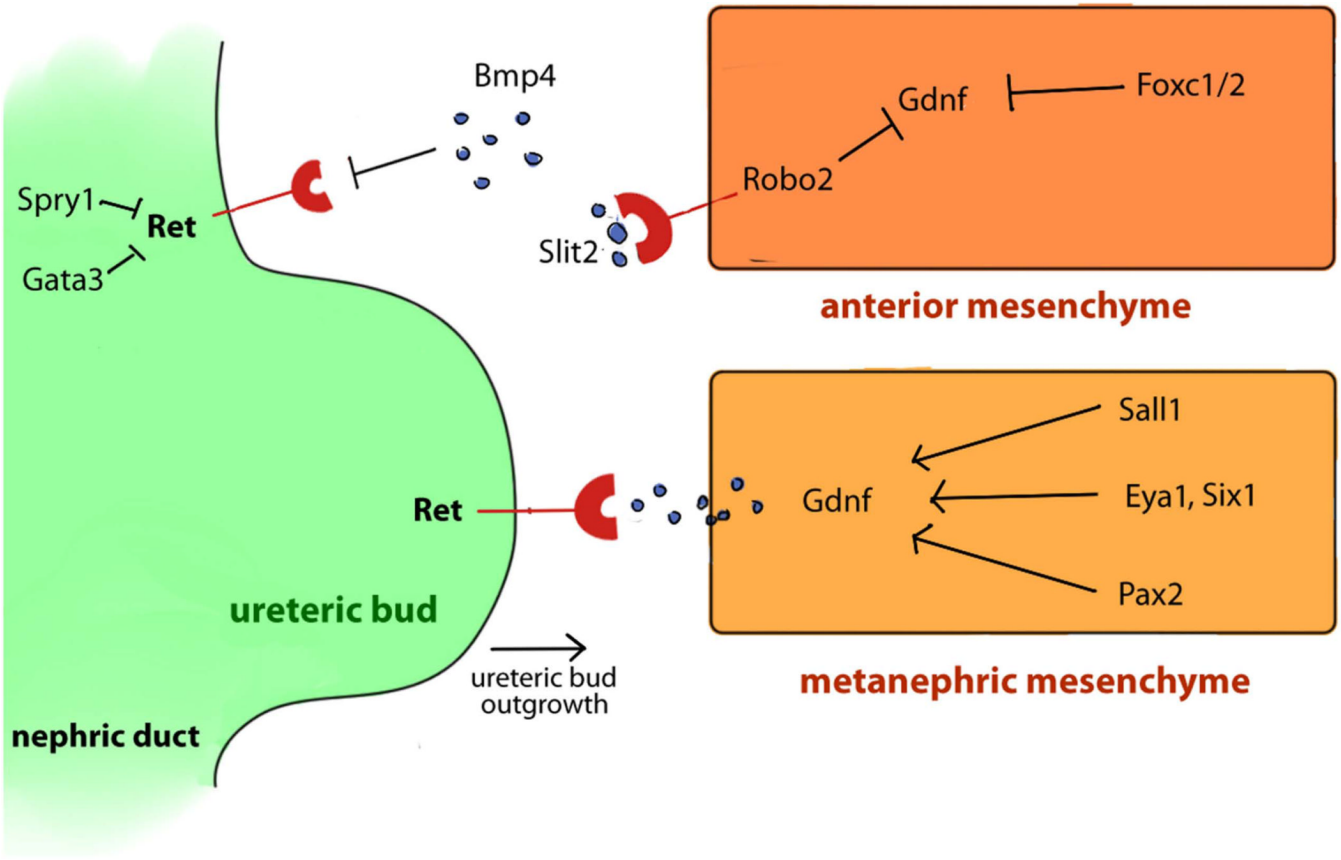

FIGURE 2.

Genes and signaling pathways involved in ureteric budding. Scheme of signaling pathways between the ureteric buds (green) and the metanephric mesenchyme (yellow-orange). The most important inducer of UB outgrowth is the Receptor Tyrosine Kinase signaling pathway mediated by Gdnf and its receptor Ret. Ret is expressed by the nephric duct (green) and ureteric buds (green). Gdnf is secreted by the metanephric mesenchyme (yellow). The coordination of different signaling pathways in the anterior mesenchyme and the metanephric mesenchyme play a crucial role in the development of a single ureteric bud.

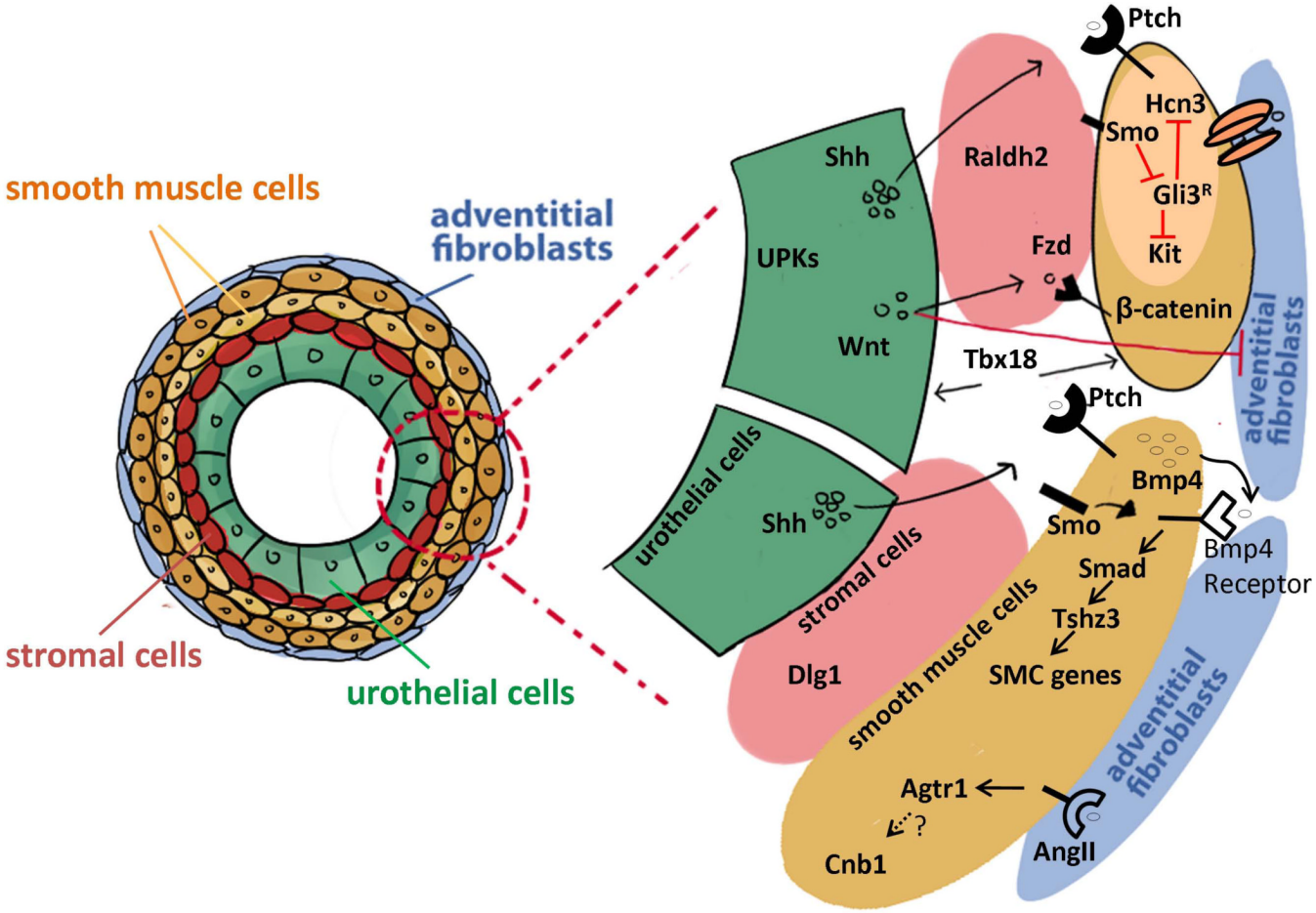

FIGURE 3.

Genes and signaling pathways involved in ureter development. Scheme of genes and signaling pathways involved in the development of the urothelial cells (green), the stromal cells (pink), the smooth muscle cells (yellow) and the adventitial fibroblasts (blue). The transcription factor Tbx18 is one of the major early genes in ureter differentiation. Tbx18 is expressed in undifferentiated ureter mesenchymal cells and promotes the differentiation of both urothelium and smooth muscle cells. Uroplakins (UPKs) are expressed on the apical surface of urothelial cells which also express Shh (sonic hedgehog) and Wnt molecules. Dlg1 plays an essential role in the differentiation of the stromal cells that express the marker gene Raldh2. The Hedgehog signaling (Shh and its receptor Ptch) plays a major role in the ureteric smooth muscle maturation through molecules in the TGF-β signaling pathway such as Bmp4 and Tshz3. Shh is also necessary for the differentiation of ureteric pacemaker cells by suppressing the Gli3 repressor ($Gli3^R$) through Smo (Smoothened) which in turn activates the expression of Kit and Hcn3. The canonical Wnt signaling is necessary for the differentiation of smooth muscle cells and the repression of the adventitial fibroblast cell differentiation. The smooth muscle cells express the Wnt receptors Frizzled (Fzd) which activates β-catenin (Ctnnb1). Calcineurin b1 (Cnb1) is required in the mesenchyme and smooth muscle cells for the development of pyeloureteral peristaltic machinery. The Angiotensin pathway may activate Cnb1.

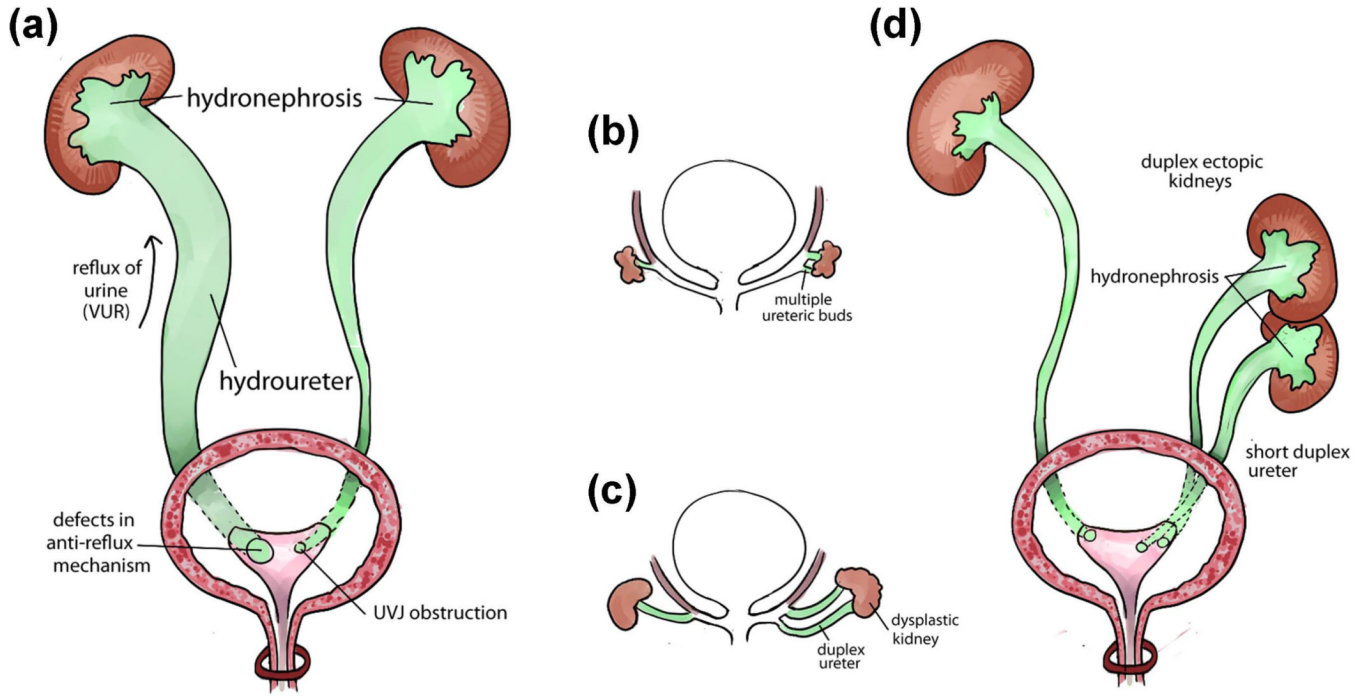

FIGURE 4.

Common congenital anomalies of the ureter. (a) Two main causes of hydronephrosis and hydroureter: vesicoureteral reflux (VUR) caused by defects of anti-reflux mechanism is on the left side and urinary obstruction caused by abnormal structure of the ureterovesical junction (UVJ) is on the right side. (b–d) Early abnormal ureteric budding can lead to congenital anomalies of the ureter: Abnormal multiple ureteric buds formation from the right Wolffian duct (b) can lead to abnormal phenotypes including duplex ureter, dysplastic kidney (c), ectopic kidney, duplex kidney, duplex ureter, short ureter, which are often associated with hydronephrosis phenotype on the right side (d), compared to the normal ureteric buds development on the left side. Each of these malformations can be found separately or coexist with other types of anomalies.

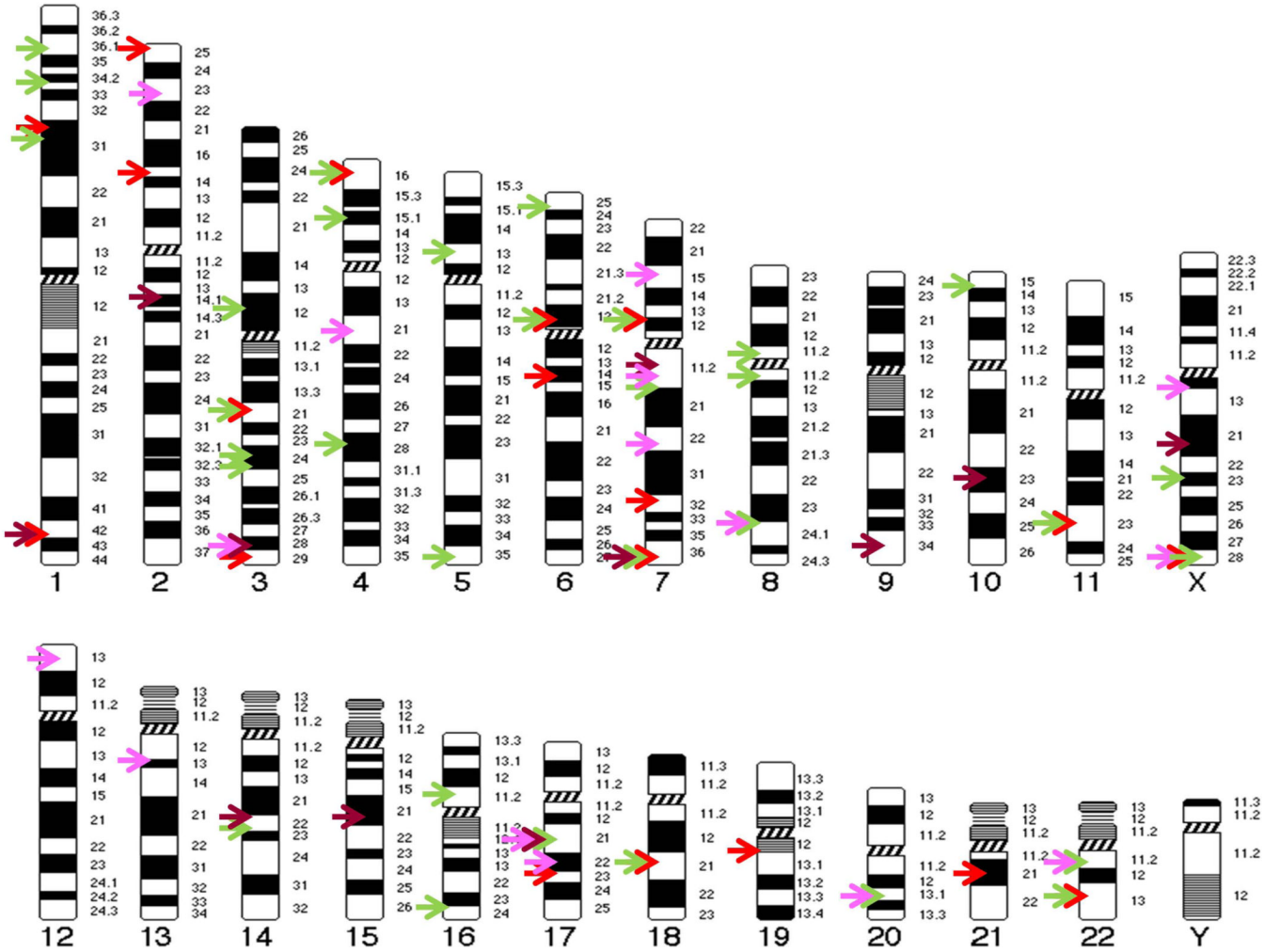

FIGURE 5.

Chromosome map of genomic loci associated with congenital anomalies of the lower urinary tract. Each arrow indicates the physical mapping position of a single locus. Different malformations are represented by different colors as following: hydronephrosis (Red), vesicoureteral reflux (Green), bladder anomalies (Brown), urethra anomalies (Purple). See Table 1–4 for details about gene names, chromosome locations, and associated phenotypes, etc.

Table 1

Genes Associated with Vesicoureteral Reflux

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	Urinary tract defects in animal models	Ref
Kal1	Xp22.31		Adhesion molecule		Kallmann syndrome (OMIM 308700)		283
Nfia	1p31.3-p31.2	ue, um	Transcription factor		Chromosome 1p32-p31 deletion syndrome (OMIM 613735): VUR	Duplex ureters, VUR, UPJ defects, hydroureter, hydronephrosis, megaureter	284
Rpl11	1p36.1-p35		Ribosomal protein		Diamond-Blackfan anemia 7 (OMIM 612562): VUR, horseshoe kidney		285
Robo2	3p12.3	mm	Slit receptor, Ig superfamily	Robo/Slit	Vesicoureteral reflux 2 (OMIM 610878)	Ectopic UB, multiple ureters, hydroureter, hydronephrosis	10, 119
Nipbl	5p13.2		chromosomal adherin		Cornelia de Lange syndrome 1 (OMIM 122470): VUR		286
Nsd1	5q35		nuclear receptor		Sotos syndrome (OMIM 117550): VUR		287
Gli3	7p13		zinc finger	hedgehog	Pallister-Hall syndrome (OMIM 146510): VUR	Peristalsis defect, hydroureter, and hydronephrosis	76, 288
Micro-deletion	7q11.2-q21.3				EEC1 syndrome (OMIM 129900):; VUR ureterocele and atretic ureter in the ectrodactyly, ectodermal dysplasia, and cleft lip/palate		289
Micro-deletion Fgfr1	8p11.23-p11.22				Kallmann syndrome 2 (OMIM 147950): VUR and ureter duplication		283
Sox17	8q11.23	ub, mm	HMGbox transcription factor		VUR3 (OMIM 613674)		138
Trps1, Ext1	8q24.11-q24.13				Langer-Giedion syndrome (OMIM 150230): VUR		290
Ret	10q11.21		Receptor	RTK	VUR, hydronephrosis, renal dysplasia		140, 141
Pax2	10q24	wd, ue, mm	Transcription factor		Papillorenal syndrome (OMIM 120330)	Caudal ureteric bud, reflux, hydroureter	291
Fgfr2	10q26.13		FGF receptor			VUR	122
Upk2	11q23	uro	Trans-membrane glycocalyx component			VUR, hydroureter, hydronephrosis	28
Six1	14q23.1		Transcription activator		Deafness, autosomal dominant 23 (OMIM 605192): VUR		155, 180, 292

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	Urinary tract defects in animal models	Ref
Micro-deletion	16p11.2				VUR, dilation and tortuosity of the ureter, (OMIM 613444)		293
Micro-deletion	17q21.31				Mental retardation, autosomal dominant 17 (OMIM 610443): cryptorchidism, hypospadias, VUR, duplex kidney		294
Sall4	20q13.2		Transcription factor		Duane-radial ray syndrome (OMIM 607323): VUR and bladder diverticula		295
Micro-deletion	22q11.2				Opitz GBBB syndrome (OMIM 145410): VUR and hypospadias		296
Upk3a	22q13.31	uro	Transmembrane glycocalyx component			VUR, hydroureter, hydronephrosis	27

Abbreviations: Chr: chromosomal location; Exp: expression in the urinary tract; Signaling: signaling pathway; Ref: References; ue: ureteric epithelium; um: ureteric mesenchyme; smc: smooth muscle cells; UVJ: ureterovesical junction; uro: urothelium; TGF-β: transforming growth factor-β; UPJ: ureteropelvic junction; VUR: vesicoureteric reflux; wd: Wolffian duct; ub: ureteric bud; RAS: Renin-angiotensin system.

Table 2

Genes Associated with Hydronephrosis and Hydroureter due to Lower Urinary Tract Defects

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	Urinary tract defects in animal models	Ref
L1cam	Xq28	ue	Adhesion molecule			Ectopic UB, duplex ureters, megaureter, hydronephrosis	297
Agtr2	Xq22-q23	um	G-protein coupled angiotensin II receptor	RAS	X-linked mental retardation-88 (OMIM 300852)	Ectopic UB, duplex ureters, hydroureter, hydronephrosis	82
Ptprf	1p34		Receptor Tyrosine Phosphatase			Hydroureter, hydronephrosis, and ureterocele	178
Nfia	1p31.3-p31.2	ue, um	Nuclear Factor 1 transcription factor		Chromosome 1p32-p31 deletion syndrome (OMIM 613735): VUR	duplex ureters, VUR, UPJ defects, hydroureter, hydronephrosis, megaureter	284
Agt	1q42.2	k	Secreted angiotensinogen	RAS		Peristalsis defect, hydronephrosis	298
Id2	2p25	ue, um	bHLH DNA binding factor	ID		UPJ defect, hydronephrosis	299
Ppp3r1	2p15	um	Protein phosphatase			Peristalsis defect, hydronephrosis	193
Hoxd13	2q31.1		Transcription factor	Wnt		Hydroureter and hydronephrosis	300
Robo2	3p12.3	mm	Slit receptor, Ig superfamily	Robo/Slit	Vesicoureteral reflux 2 (OMIM 610878)	Ectopic UB, multiple ureters, hydroureter, hydronephrosis	10, 119
Ctnnb1	3p21		β-catenin	Wnt		Hydroureter and hydronephrosis	301
Rarb2	3p24.2	ue	Retinoic acid receptor	Retinoic acid signaling		Ectopia of distal ureter ends, hydroureter, megaureter, hydronephrosis	43
Gata2	3q21.3	ue, um	Zinc Finger transcription factor	Wnt		Megaureter, hydroureter, hydronephrosis, hypoplastic kidneys	302
Agtr1a/b	3q24	um	Angiotensin 2 receptor	RAS		Peristalsis defect, hydroureter, hydronephrosis, pelvis agenesis	199
Dlg1	3q29	ue, um	Membrane-associated guanylate kinase scaffolding protein	p38		Congenital hydronephrosis, smooth muscle orientation defect, peristalsis defect	190
Slit2	4p15.2	ue	Secreted protein -Robo ligand	Robo/Slit		Ectopic UB, multiple ureters, hydroureter, hydronephrosis	119
Wfs1	4p16.1		transmembrane protein		Wolfram syndrome (OMIM 222300): hydronephrosis, dilated ureters, distended bladder without VUR		303
Scarb2	4q21.1		glycoprotein			Kidney and ureter duplication, UPJ obstruction, hydroureter, and hydronephrosis	304

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	Urinary tract defects in animal models	Ref
Spry1	4q28.1	wd, mm	Receptor Tyrosine Kinase antagonist	GDNF/RET		Ectopic UB, multiple ureters, hydroureter, hydronephrosis	120
Bmp5	6p12.1	um	Secreted molecule	TGF-beta		Hydroureter, hydronephrosis	305
Foxc1	6p25	um	Forkhead transcription factor	Foxc	Axenfeld-Rieger syndrome type 3 (OMIM 602482)	Ectopic UB, duplex ureters, hydroureter, hydronephrosis	121, 174
Unknown gene	6p				Multicystic renal dysplasia, bilateral; MCRD (OMIM 143400): UPJ obstruction, hydronephrosis		306
Tbx18	6q14-q15	um	T-box transcription factor	Bmp, wnt, hedgehog		Lack of smooth muscles in the ureter, short ureter, hydronephrosis	29
Gli3	7p13		zinc finger	hedgehog	Pallister-Hall syndrome (OMIM 146510)	peristalsis defect, hydroureter, and hydronephrosis	76, 288
Smo	7q32.3		G protein-coupled receptor	Hedgehog		Ureter dyskinesia, functional obstruction, hydroureter and hydronephrosis	76
Shh	7q36	ue	Secreted Sonic Hedgehog	Hedgehog		Smooth muscle defects, short hydroureter, hydronephrosis	32
Ret	10q11.21		Receptor	RTK	Hydronephrosis, megaureters, renal dysplasia	Abnormal distal ureter maturation	43, 141
Upk2	11q23	uro	Transmembrane glycocalyx component			VUR, hydroureter, hydronephrosis	28
Aqp2	12q12-q13		Water channel protein			Hydronephrosis	187
Bmp4	14q22-q23	um	Secreted molecule-TGF-beta family	TGF-beta	Renal hypoplasia	Ectopic UB, duplex ureters, ectopic UVJ, hydroureter	77
Aldh1a2	15q21.3		Retinaldehyde dehydrogenase			Urogenital sinus abnormalities hydronephrosis and megaureter	44
Stra6	15q24.1		A receptor for retinol/retinol binding protein complexes	Retinoic acid signaling	Hydronephrosis		307
Foxc2	16q24.1	um	Forkhead transcription factor	Foxc		Ectopic UB, duplex ureters, hydroureter, ureter agenesis	121
Rara	17q21.2		Retinoic acid receptor	Retinoic acid signaling		Ectopia of distal ureter ends, hydroureter, megaureter	43, 44
Smad4	18q21.1	ue, um		TGF-β		Hydroureter, hydronephrosis	79
Tshz3	19q12		Transcription factor	Hedgehog		Smooth muscle differentiation, congenital hydronephrosis	31

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	Urinary tract defects in animal models	Ref
Adamts1	21q21.2	um	Secreted protease			enlarged renal calices; ureteropelvic junction obstruction	308
Upk3a	22q13.31	uro	Trans-membrane glycocalyx component			VUR, hydroureter, hydronephrosis	27
Unknown gene					Hardihar syndrome (OMIM 612726): hydroureter, hydronephrosis		309
Unknown gene					Fryns syndrome (OMIM 229850): Cryptorchidism, megaureter, hydroureter, cystic ureter, ectopic or blind urethral opening		310

Abbreviations: Chr: chromosomal location; Exp: expression in the urinary tract; Signaling: signaling pathway; Ref: References; k: kidney; ue: ureteric epithelium; um: ureteric mesenchyme; uro: urothelium; TGF-β: transforming growth factor-β; UPJ: ureteropelvic junction; VUR: vesicoureteric reflux; RAS: Renin-angiotensin system.

Table 3

Genes Associated with Bladder Malformations and Dysfunctions

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	Urinary tract defects in animal models	Ref
Atp7a	Xq21.1		Transmembrane copper-transporting P-type ATPase		Occipital horn syndrome (OMIM 304150): bladder diverticula		236
Chrm3	1q43		Muscarinic acetylcholine receptor		Prune Belly syndrome (OMIM 100100)	Male distended bladders, impaired contractility of the detrusor smooth muscle	230, 231
Gli2	2q14		Transcription factor	Hedgehog		Hypoplasia of the internal urethra and bladder	52, 94, 311, 312
Tp63	3q28	bl, uro	Transcription factor			bladder exstrophy	219
Micro-deletion	7q11.23				Williams syndrome (OMIM 194050): urethral stenosis, bladder diverticula, vesicoureteral reflux		239, 240
Shh	7q36	uro	Secreted Sonic Hedgehog	Hedgehog		hypoplasia of external genitalia, internal urethra (pelvic urethra) and bladder	94
Hpse2	10q23-q24		Heparanase		Urofacial syndrome (OMIM 236730)		248
Atca2	10q23.31		actin		Prune-belly sequence		313
Aldh1a2	15q21.3		Retinaldehyde dehydrogenase			Urogenital sinus abnormalities hydronephrosis and megaureter	44
Col5a2, Col5a1, Col1a1	2q14-q32 9q34.2-q34.3 17q21.33		Collagen		Ehlers-Danlos syndrome (OMIM 130000)		241, 242
Ltbp4	19q13		latent TGF-β -binding protein	TGF-β	Cutis laxa syndrome with severe pulmonary, gastrointestinal, and urinary abnormalities" (OMIM 613177): bladder diverticula, hydronephrosis		243
Microduplication	22q11.21		Myosin		Bladder exstrophy		217, 218
Ubp1	22q11.23		Beta-ureidopropionase		Beta-ureidopropionase deficiency (OMIM 606673): has bladder exstrophy phenotype		314

Abbreviations: Chr: chromosomal location; Exp: expression in the urinary tract; Signaling: signaling pathway; Ref: References; bl uro: bladder urothelium; m: mesenchyme; uro: urothelium; TGF-β: transforming growth factor-β.

Table 4

Genes and Genomic Loci Associated with Urethra Anomalies

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	urinary tract defects in animal models	Ref
Ar	Xq12		Androgen receptor		Hypospadias (OMIM 300633)		315
Mid1	Xp22		RING finger protein		Opitz syndrome (OMIM 300000): hypospadias		316
Mamld1	Xq28		transcriptional co-activator		Hypospadias 2, X-linked (OMIM 300758)		317
EphB2	1p36.1-p35		Ephrin receptor			Hypospadias	318
Srd5a2	2p23		Steroid 5-alpha-reductase		Pseudovaginal perineoscrotal hypospadias (OMIM 264600)		319
Tp63	3q28	up	Transcription factor		Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (OMIM 604292) and split-hand/foot malformation 4 (OMIM 605289)	Hypospadias	320, 321
Fras1	4q21.21	ub	putative extracellular matrix protein		Fraser syndrome (OMIM 219000): anterior urethral atresia	Dilated ureteric bud, cystic kidney	322, 323
Dlx5, Dlx6	7q22	up	Transcription factor			Hypospadias	321
Gli3	7p13		zinc finger	hedgehog	Pallister-Hall syndrome (OMIM 146510)		76, 288
Hoxa13	7p15.2		Transcription factor	Wnt	Hand-foot-uterus syndrome (OMIM 140000): duplication of the genital tract in female and hypospadias in male		324
Microdeletion	7q11.23				Williams syndrome (OMIM 194050): urethral stenosis, bladder diverticula, VUR		239, 240
Shh	7q36	uro	Secreted Sonic Hedgehog	Hedgehog		hypoplasia of external genitalia, internal urethra (pelvic urethra) and bladder	94
Pitx2	4q25		Transcription factor		Axenfeld-Rieger syndrome, type 1 (OMIM 180500): hypospadias		325
Eya1	8q13.3		Transcription activator			Hypospadias, hypoplastic genitalia and persistent cloaca	257
Plec	8q24		Intermediate filament-binding protein		Epidermolysis Bullosa (OMIM 226670): urethral strictures		326
Gata3	10p15		Transcription factor	Wnt	Hypoparathyroidism-deafness-renal syndrome (OMIM 146255)	Ectopic UB, duplex kidneys, enlargement of the vas deferens, loss of uterus	154
Fgfr2	10q26.13		FGF receptor			Hypospadias	327
Fkbp4	12p13.33		Macro immunophilin			Hypospadias	328
Frem2	13q13.3		Membrane protein- Fras1 family		Fraser syndrome (OMIM 219000): anterior urethral atresia	Renal cysts	322, 329

Gene	Chr	Exp	Type of protein	Signaling	Human disease (OMIM)	urinary tract defects in animal models	Ref
Six1	14q23.1		Transcription activator			Hypospadias, hypoplastic genitalia and persistent cloaca	257
Wnt3	17q21		Secreted protein	Wnt	Tetraamelia (OMIM 273395): urethra atresia, persistence of cloaca		330
Mks1	17q22		Basal body protein	Hedgehog	Meckel syndrome type 1 (OMIM 249000): urethral atresia	Renal cysts	331, 332
Bmp7	20q13	up	Secreted protein TGF-β family	TGF-β		Hypospadias	321
Bbs					Bardet-Biedl syndrome (OMIM 209900): persistent urogenital sinus, ectopic urethra in female BBS patients		333
Unknown gene					Cervical ribs, sprengel anomaly, anal atresia, and urethral obstruction (OMIM 601389)		334
Unknown gene					Vitiligo, progressive, with mental retardation and urethral duplication (OMIM 277465)		335
Unknown gene					Fryns syndrome (OMIM 229850): Cryptorchidism, megaureter, hydroureter, cystic ureter, ectopic or blind urethral opening		310

Abbreviations: Chr: chromosomal location; Exp: expression in the urinary tract; Signaling: signaling pathway; Ref: References; up: urethral plate; TGF-β: transforming growth factor-β; VUR: vesicoureteral reflux.

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