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Genetic and developmental basis for urinary tract obstruction

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Abstract

Urinary tract obstruction results in obstructive nephropathy and uropathy. It is the most frequent cause of renal failure in infants and children. In the past two decades, studies in transgenic models and humans have greatly enhanced our understanding of the genetic factors and developmental processes important in urinary tract obstruction. The emerging picture is that development of the urinary tract requires precise integration of a variety of progenitor cell populations of different embryonic origins. Such integration is controlled by an intricate signaling network that undergoes dynamic changes as the embryo develops. Most congenital forms of urinary tract obstruction result from the disruption of diverse factors and genetic pathways involved in these processes, especially in the morphogenesis of the urinary conduit or the functional aspects of the pyeloureteral peristaltic machinery.

Keywords

Urinary tract obstruction; genetic mutation; development; obstructive nephropathy; obstructive uropathy

Introduction

Urinary tract obstruction (UTO) can lead to hydroureter, hydronephrosis, and even renal failure (1-3). It is a condition that concerns both nephrologists and urologists. In a strict sense, UTO describes the presence of a physical blockage to urine flow. However, the word “obstruction” is also used to describe the failure of urine transport from the kidney to the ureter in the absence of physical blockage. In this review, we use the word “obstruction” to describe both physical obstruction of the urinary tract as well as functional obstruction (4,5). There have been many comprehensive reviews on the pathological outcomes and treatment options for obstructive nephropathy and uropathy (2,6-10). This review focuses on the recent advances in understanding the genetic and developmental causes of UTO, especially the congenital and hereditary forms.

Diverse Causes for UTO

UTO is categorized by its location and/or cause (11) (Fig. 1). Obstruction at the junction between the ureter and the renal pelvis is called ureteropelvic junction (UPJ) obstruction presenting as hydronephrosis without obvious dilatation of the ureter. Urine blockage at the ureterovesical junction (UVJ) and the backflow of urine from the bladder to the ureter are described as UVJ obstruction and vesicoureteral reflux (VUR), respectively. Although VUR can occur along with other urinary tract anomalies, including anatomical obstruction of the

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urinary tract, UVR does not necessarily lead to upper urinary tract damage by itself. Interruption of urine flow from the bladder to the outside environment through the urethra is called bladder outlet obstruction. The presence of posterior urethral valves is the most common type of bladder outlet obstruction in male pediatric patients. Although not all of the terms described above directly describe the cause of the problem, the location of the urine flow interruption is taken into consideration in determining etiology. Obstruction can be caused by factors both within and outside the urinary system. Within the urinary system, developmental anomalies can result in anatomical blockage or stenosis of the urinary conduit, defective valves at UVJ, short intramural ureter, as well as fistulae between the ureter and surrounding structures. Since urine flow from the kidney to the bladder requires active pyeloureteral peristalsis, any developmental defects affecting the peristaltic machinery, including the pacemaker, the smooth muscle (SM), and the neuronal control, could potentially lead to functional obstruction. Hyperplasia of the urothelium and urinary tract infection (UTI) can block the ureteral lumen, causing obstruction. Renal dysfunction can also secondarily lead to urinary tract dysfunction and obstruction. For example, collecting duct defects can lead to severe polyuria that overwhelms the pyeloureteral peristaltic machinery, leading to functional obstruction. Renal tubular dysfunction can result in renal calculi and obstruction of the urine path. Factors outside the urinary system that can create spatial constraints for the urinary conduit can also lead to UTO. These include tumors, prostatic hypertrophy, aberrant vessel crossing, and pregnancy.

Besides the overt familial cases and transgenic models, strong genetic determinants were reported in UTO by a number of studies in seemingly sporadic cases (12-14). In one of these studies, Feather *et al* found a 30-50-fold increase in VUR incidence in first-degree relatives of probands with VUR, compared to the general population (13). Environmental factors can influence developmental defects in the urinary tract caused by genetic mutations, contributing to the variability of the urinary defects seen among patients or among animal models with the same genetic mutation.

Congenital UTO Originates from Anomalies in Metanephric Kidney Development

Congenital diseases originate from developmental errors and by definition, present at birth. In some cases, although the hallmarks of UTO, hydroureter and hydronephrosis may emerge at later postnatal stages, the cellular lesions and anatomical changes required for disease progression are already present at birth. In addition, hydronephrosis and hydroureter are frequently associated with a range of other kidney and urinary tract anomalies, including but not limited to, renal agenesis, renal hypoplasia, supernumerary ureters, ectopic ureters, horseshoe kidneys, pelvic kidneys, and others. Some of these defects directly cause UTO, while others reflect the commonality of defective critical developmental processes responsible for these defects. Although developmental errors in many areas may lead to UTO, three processes stand out as the most likely sources of such errors. These include the induction of the metanephric kidney, the establishment of the urinary conduit, and the maturation of the pyeloureteral peristaltic machinery (Fig. 2).

Metanephric Kidney Induction—Metanephric kidney induction occurs in the narrow strip of intermediate mesoderm (IM). In mammals, a pair of Wolffian ducts (WD, also known as mesonephric duct), connect the mesonephri (the transient embryonic kidney) to the urogenital sinus and serve as the anlage for the ureters and male reproductive ducts. During mid-gestation (at about E10.5 in mice, 28 days for human fetus), the ureteric bud (UB) emerges from the WD and invades the metanephric mesenchyme (MM) within the IM to initiate the development of the metanephric kidney (the definitive kidney). The reciprocal interactions between the UB and the MM drive the branching of the UB within the MM and the mesenchymal-epithelial transformation of the MM to form various nephron components. Anomalies in metanephric kidney induction may result in renal hypoplasia, renal agenesis, ectopic and supernumerary

ureters, and a range of other defects. Some of these defects, especially ectopic ureter and supernumerary ureters, set the stage for UTO to occur. Since kidney induction was covered by a number of recent reviews, only aspects related to later UTO will be discussed in more details here.

Glial-derived neurotrophic factor (GDNF) is one of the most important factors expressed in the MM. GDNF, along with GDNF-family receptor α1 (GFRα1), activates the tyrosine kinase receptor RET (expressed in the WD) to promote the localized UB outgrowth. Null mutations in *Gdnf*, *Ret*, or *Gfrα1* result in renal agenesis or severe dysplasia due to failure of UB outgrowth. The domain of *Gdnf* expression is tightly controlled to ensure that only one ureter will emerge from the WD at the correct position. A number of genes, including *Sal-like gene 1 (Sall1), Sine oculis homeobox homolog 1 (Six1), Eyes-absent homolog 1 (Eya1), Paired-box 2 (Pax2), Growth and differentiation factor 11 (Gdf11), Hox11* genes, and others, directly or indirectly regulate the expression of *Gdnf* to ensure normal UB induction (15-22). *Forkhead box protein c1/c2 (Foxc1/c2)* and *Slit homolog 2 (Slit2)/Roundabout homolog 2 (Robo2)*, however, suppress the expression of *Gdnf* in the region anterior to the MM. Disruption of these genes leads to the anterior expansion of the *Gdnf* expression domain and the formation of supernumerary and ectopic ureters (15,16,23,24) (Fig. 2A). Both *in vitro* treatment of the cultured WD by GDNF or the transgenic expression of *Gdnf* in the WD can result in multiple ureters (25). However, renal agenesis in $Gdnf^{-/-}$ mice can be largely rescued by transgenic expression of *Gdnf* throughout WD (with no positional information for UB budding). This and other findings suggest the existence of redundant inductive signals for the localized induction of UB (25,26). In particular, the Fibroblast growth factor (Fgf) signaling appears to have functions in both the UB and the MM during kidney induction and later development (27). Interruption of Fgf signaling in these embryonic structures can lead to a range of urinary tract anomalies, including UTO (28).

RET signaling in WD and UB appears to have a number of downstream pathways affecting metanephric development in different ways (29). While the null mutations and a mutation targeting a tyrosine linked to MAPK activation generally lead to renal agenesis, mutations targeting other tyrosine phosphorylation sites cause a range of congenital anomalies of the kidneys and the lower urinary tract, including supernumerary ureters, hydroureter, and hydronephrosis (29,30). Furthermore, the tyrosine kinase inhibitor Sprouty 1 (SPRY1) suppresses RET activation in the WD, and is also important for ensuring the correct number and position of UB outgrowth (31,32). Loss of *Spry1* function leads to the development of supernumerary and obstructed ureters (31). *Bone morphogenetic protein 4* (*Bmp4*) is expressed in the mesenchyme surrounding the WD and negatively regulates UB budding. Gremlin 1 (GREM1), an inhibitor of BMP signaling, is produced by MM to counter the BMP4 suppression and to promote UB budding. Therefore, inactivating mutations of *Bmp4* and over-activation of *Grem1* can both lead to the formation of supernumerary ureters that are frequently obstructed (33-35) (Fig. 2A).

Disruption of UB initiation and MM survival generally leads to renal agenesis, while anomalies in UB position and number create abnormal connections between the ureter and the bladder, leading to UTO (discussed in the next section). Different mutations of the same gene or even the exact same mutation can lead to different phenotypic and clinical presentations (even on two sides of the same individuals), underlying the intricate connection of these processes (36-38). The concurrence of renal agenesis/dysplasia and UTO in the same individuals and the variability of the disease presentation may seem enigmatic at first. Better understanding of the metanephric kidney development has provided more reasonable explanations for such phenomena. In a hypothetical example, a mutation affecting the timing and positioning of UB budding, may slow UB budding to a level that UB barely reaches the MM in time to prevent its apoptosis. Mispositioning of the UB then leads to ectopy and UTO. However, any additional

factors, including intrinsic variations or random extrinsic disturbances, may delay the UB further, causing the failure of the UB to reach MM before its degeneration and leading to renal agenesis. Thus a quantitative difference (slower UB outgrowth, for example) may be translated into qualitative outcomes, leading to concurrence of seemingly distinct defects (renal agenesis or UTO) in affected individuals.

Establishment of the Urinary Conduit—Although defective kidney induction is the primary cause in many cases of congenital UTO, later remodeling of the lower urinary tract, especially the connection of the ureter to the bladder, also plays an important role in ensuring the proper layout of the urinary conduit system (36,39-42). As development proceeds, the UB becomes the ureteric epithelium and the collecting duct system in the kidney (15,16). The bladder, on the other hand, develops independently from the urogenital sinus of an endodermal origin. These two organs have to join precisely for completion of the urinary path. The complexity of this joining process and the demanding anti-reflux requirement near the junction are likely the reasons for the high incidence of VUR and UVJ obstruction.

The process of establishing the ureter-bladder connection has been redefined in unprecedented clarity and detail in a series of recent studies (36,39,41). These studies showed that the maturation of the ureter is a multi-step process. After emerging from the WD, the UB/ureter moves caudally along the common nephric duct (CND) toward the urogenital sinus (the future bladder). This is followed by lateral movement of the ureter toward its final insertion site away from the WD. Apoptosis of the CND eventually severs the link between the ureter and the WD (Fig. 2B). It appears that *Ret* has an additional site of action in the trigonal wedge area for the normal migration of the ureter. *Ret* expression in this area is itself regulated by Vitamin A through the RARA/RARB2 receptors. CND apoptosis is also dependent on Vitamin A. Disruption in *Ret*, *Retinoic acid receptor alpha* (*Rara*)*/ Retinoic acid receptor beta 2* (*Rarb2*), and *Aldehyde dehydrogenase 1 family, member A2* (*Aldh1a2*) (encodes an enzyme in retinoic acid synthesis) can lead to abnormal connection of the ureter to the bladder and UTO (36,39). In some of these mice, the ureter connects to the reproductive tract as the normal separation of the ureter orifice from the WD is disrupted. A couple of studies have shown that the inactivation of *Discs large homolog 1* (*Dlgh1*) causes hydronephrosis and hydroureter during embryonic development (43,44). The study by Iizuka-Kogo et al found that the ureteral orifice of some of these mutants failed to migrate down the CND to reach the bladder and others have abnormally formed connections to the bladder, causing UTO in both cases (44). Additional functions of *Dlgh1* in the differentiation and organization of the ureteral SM cells (SMCs) was indicated in another study by Mahoney et al and will be discussed in the next section on the maturation of the peristaltic machinery (43). Even a delayed separation of the ureter from the WD, as found in the $Pax2^{1Neu/+}$ mice (45), may cause reversible VUR, providing one possible explanation for pediatric VUR that resolves overtime. The intravesical section of the ureter is usually compressed by the surrounding bladder muscle. It appears that the intravesical ureter length can be affected by genetic mutations and is inversely correlated to the risk of reflux (46). In addition, inactivation of *Nuclear factor I/A* (*NFIa*) causes both UVJ and UPJ anomalies in murine models and humans, revealing the importance of this gene in the correct formation of these important junctions (47).

The trigone is a triangular muscular structure on the bladder floor important for the anti-reflux mechanism. It is believed to be critical in the control of the ureter position and the proper function of the ureteral valves. Traditional models described the origin of the trigone as the expansion of the CND. Recent findings, however, indicate that the trigone is not derived from the CND that undergoes apoptosis (39). Instead, the trigone develops from the intercalation of the bladder and the ureter SMCs with the bladder SMCs being the vast majority (41). The detailed mechanism of ureteral valve formation is still unclear. However, it appears that a transient membrane structure (Chwalla's membrane) seals the distal end of the ureter (48). It

ruptures to allow urine flow after the ureter is properly inserted into the bladder. Although there is no evidence that the Chwalla's membrane contributes to the valves, its normal rupture and the development of the valves are likely temporally and spatially coordinated. Delayed rupture of the Chwalla's membrane could lead to UTO.

Maturation of the Pyeloureteral Peristaltic Machinery—The correct layout of the urinary conduit does not by itself guarantee uninterrupted urine flow. Urine transfer from the kidney to the bladder is an active process requiring well coordinated pyeloureteral peristalsis. Unidirectional peristalsis is believed to be initiated by the pacemaker cells. Although not very much is known about these cells, evidence suggests that they are likely specialized SMCs in the renal pelvis (49). The peristalsis itself is powered by the SMCs in the pelvis and ureter. SM defects have been frequently associated with UTO and the development of the ureteral SM will be discussed in more details below. Among other factors that may regulate peristalsis is neuronal control. The ureteral wall is highly innervated. Although neurological dysfunction can cause neurogenic bladder that loses the proper control of the expulsion of the stored urine from the bladder to the external environment through the urethra, the role of neuronal control of pyeloureteral peristalsis is less clear. Spontaneous peristalsis in the isolated or denervated pyeloureteral complexes retains characteristics similar to those observed *in vivo* and is not blocked by tetrodotoxin or other neuronal blockers (49,50). In renal transplantation, donor kidney and ureter are surgically ligated to the recipient bladder. Effective peristalsis occurs shortly after surgery with no evidence of immediate reinnervation. These observations suggest that ureteral motility is largely a myogenic process, though the innervating nerves may have a modulatory role (49,50).

While the ureteral epithelium is derived from the UB, the associated mesenchyme originates from the tailbud mesenchyme (40). The subdivision of the UB into the intra-renal colleting duct system and the ureter with its associated SM creates another junction within the urinary system where progenitors of distinct embryonic origins have to precisely integrate to form a functional structure. The complexity involved in such integration, similar in this regard to the situation at the UVJ, may increase the probability for errors to occur, leading to the high incidence of UPJ obstructions in humans and animal models. *Bmp4*, expressed in the tailbud mesenchyme, is essential for these cells to participate in the formation of the ureteral SM. Spatially restricted *Bmp4* expression determines the site where UB is divided into the collecting duct system and the ureter (40). Thus, *Bmp4* has an important role in regulating UB budding and in ureteric mesenchyme differentiation, both directly relevant to UTO when errors occur. *T-box transcription factor 18* (*Tbx18*) is specifically expressed in the ureteric mesenchyme. Inactivation of *Tbx18* leads to the loss of *Bmp4* expression in the ureteral mesenchyme and defective differentiation of the mesenchymal cells into functional SMCs (42). If *Bmp4* is indeed controlled by *Tbx18*, *Tbx18* may be the key factor in the division of the UB into the collecting duct system and the ureter along the anterior and posterior axis (51).

Development of the ureteral mesenchyme is also regulated by the ureteral epithelium. Inactivation of *Sonic hedgehog* (*Shh*) in the urothelium leads to defective ureteral mesenchyme differentiation and hydroureter (52). *Bmp4* expression is lost in these mutants, suggesting that Shh in the urothelium is required to sustain *Bmp4* expression in the ureteral mesenchyme, presumably through the Shh receptor Ptch that is expressed in the periureteral mesenchyme. The transcription factor *Teashirt zinc finger family member 3* (*Tshz3*) is expressed in the ureteric mesenchyme and its inactivation results in defective ureteral SM differentiation and hydronephrosis (53). *Shh* and *Bmp4* expression appear normal in these mutants, suggesting that *Tshz3* may function downstream of these factors for the regulation of SM differentiation. *Dlgh1* is expressed more strongly in the epithelium than in the mesenchyme. Its inactivation results in a range of urogenital defects, including defective ureteral insertion into the bladder as discussed in the previous section (43,44). In addition, Mahoney et al described the absence

of a stromal cell layer between the urothelium and the SM as well as the misalignment of the muscle layers that affects peristalsis (43).

The Renin-Angiotensin system (RAS) is known to be involved in renal injury as a result of UTO. RAS, however, has a constructive role during urinary tract development (54,55). Mutations in a number of RAS component genes cause congenital anomalies of the kidney and urinary tract (CAKUT), including UTO. Inactivation of *Angiotensin II receptor, type 2* (*Agtr2*) results in CAKUT with partial penetrance (56,57). Loss of *Angiotensin II receptor, type 1a/b* (*Agtr1a/b*) also results in pathological changes in the kidney resembling obstructive nephropathy (58,59). Similar findings were reported in the study of mutant alleles of the other RAS components *Angiotensin converting enzyme* (*Ace*) (60) and Angiotensinogen (*Agt*) (61, 62). Although the broad effect of RAS in blood pressure control and regulation of the ability to concentrate urine may contribute to the observed renal pathological changes, evidence suggests that direct function of RAS in the ureteral SM differentiation plays an important role (58). Calcineurin, a calcium-dependent serine/threonine phosphatase, dephosphorylates the cytoplasmic Nuclear Factor of Activated T-cells (Nfat) transcription factors (among a number of its known substrates) and sends them into the nucleus to activate the transcription of the downstream genes. In our previous study, inactivation of Calcineurin in the metanephric and ureteric mesenchyme leads to the underdevelopment of the urinary tract SMs and results in dysfunction of the pyeloureteral peristaltic machinery (4). Our recent studies indicate that transgenic activation of *Nfatc1* in the urinary tract also leads to severe developmental anomalies including hydroureters and hydronephrosis (Wang and Chen, unpublished results), emphasizing the importance of the Calcineurin-Nfat pathway in the regulation of the normal development of the urinary system. A number of studies suggest that RAS can induce activation of Calcineurin. It is likely that within the urinary system, RAS activates Calcineurin to induce Nfat-mediated transcription for proper urinary tract development and differentiation.

Other Developmental Defects Causing UTO—Besides the processes described above, UTO can also be caused by a variety of developmental anomalies. Inactivation of either *Uroplakin II* (*UpkII*) or *Uroplakin III* (*UpkIII*) causes defective plaque formation and hyperplasia of the urothelium (63,64). These mutants have UTO possibly caused by urothelial hyperplasia blocking the urinary path, a situation similar to the dioxin-induced hydronephrosis (65). Interestingly, autoimmune antibodies against UpkIII and hydronephrosis were found in mice doubly homozygous for mutations in the following two genes: *Fc receptor, IgG, low affinity IIb* (*Fcgr2b*) and *Programmed cell death 1* (*Pdcd1*) (66). Hydronephrosis was also observed in >50% of mice overexpressing *Interleukin 9* (*IL-9*) (67). Autoimmune antibodies were again found in these mice, though the specificity of these antibodies was not well characterized. Linkage to *human leukocyte antigen* system (*HLA*) was reported in humans with UTO (68,69). Whether autoimmunity plays a role in these patients is not known.

Besides factors that directly affect the cells and tissues in the urinary conduit, renal dysfunction can also cause UTO. Poorly controlled polyuria can lead to hydronephrosis in humans. This is also exemplified in the classical *cph* (*Congenital progressive hydronephrosis*) mutant mice. These mice have a single amino acid substitution in the water channel protein Aquaporin 2 (AQP2) that prevents its normal trafficking to the apical membrane for water absorption. The resulting polyuria overwhelms the pyeloureteral peristaltic machinery and leads to progressive hydronephrosis (70). Hydronephrosis is a common prenatal diagnosis that frequently resolves spontaneously (2). Since urine output is highly variable and influenced by multiple factors, it is conceivable that temporary polyuria may contribute to some of these spontaneously resolved hydronephrosis cases. Another example of renal dysfunction causing UTO is the *Solute carrier family 7 member 9* (*Slc7a9*)$^{-/-}$ mice that have cystine urolithiasis, causing obstruction by blocking the ureteral lumen (71).

Summary

It is becoming clear that UTO can result from a wide variety of environmental causes or genetic mutations. Even the subtypes of UTO (such as UPJ obstruction, UVJ obstruction, etc) are heterogeneous and may have drastically different etiology. Kidney and urinary tract diseases frequently have ambiguous pathological presentations and require an understanding of the primary molecular and cellular defects to uncover the true nature of the condition. Although great progress has been made in understanding the genetic and developmental basis of UTO, to pinpoint the etiology in a given patient remains a great challenge. Further investigation is necessary to translate the knowledge gained in these studies into improvements in diagnosis and treatment.

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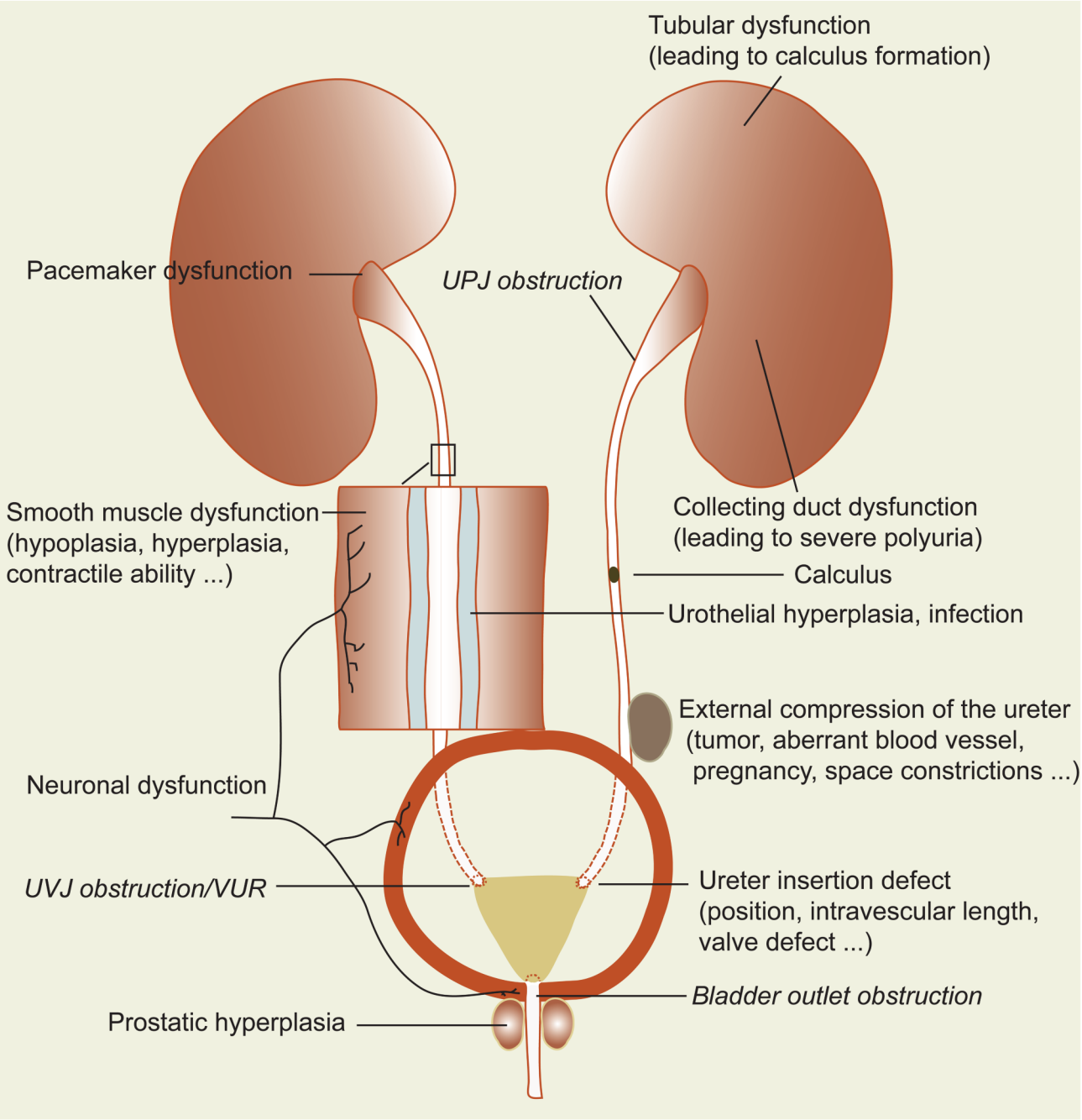

Figure 1. Causative factors for UTO

UPJ, UVJ, and bladder outlet obstructions are in Italics as these terms describe the location but not the causes for the obstruction.

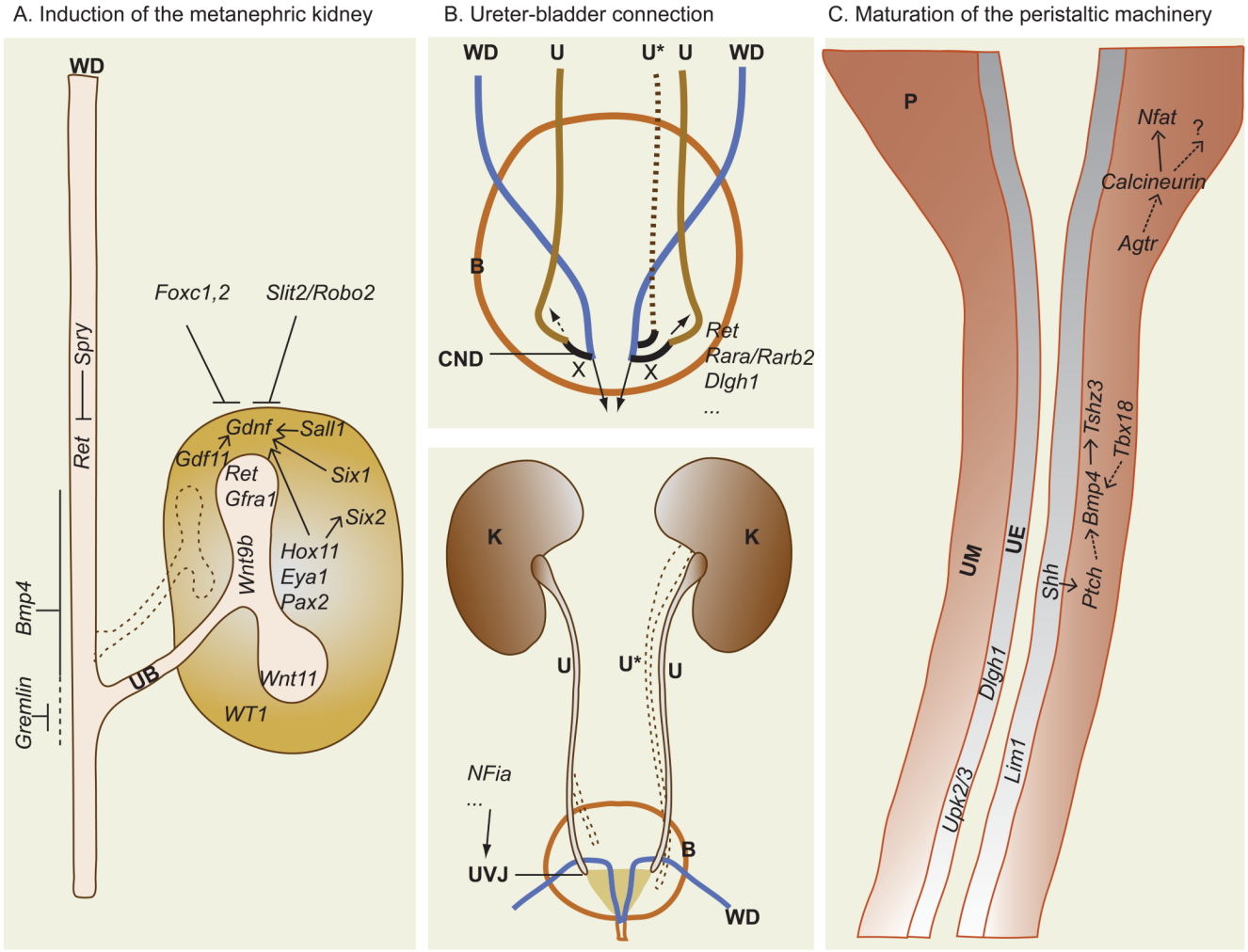

Figure 2. Key developmental steps in which errors frequently lead to UTO

A, Metanephric kidney Induction. WD: Wolffian duct. UB: Ureteric bud. **B**, Ureter-bladder connection. K: Kidney. U: Ureter; U*: Eectopic/supernumerary ureter (dotted lines); CND: Common nephric duct. B: Bladder. X: indicates that the CND undergoes apoptosis so that the ureter separates completely from the WD. The dotted arrow in the top panel indicates abnormal migration/positioning of the ureter that can result in abnormal insertion of the ureter into the bladder. In the bottom panel, the dotted lines connected to the right ureter depict the abnormal positioning of the ureter when the ureter insertion process is affected. The dotted lines on the left side depict the ectopic supernumerary ureter. Both diagrams in **B** represent the ventral views of the urinary system. **C**, Maturation of the pyeloureteral peristaltic machinery. P: Pelvis, UM: Ureteric mesenchyme; UE: Ureteric epithelium. Dotted arrows indicate potential regulation.

Table 1
Genetic mutations causing congenital UTO

The gene names follow the terminology in the original reference. Newer names are listed in the second column. The known or predicted function of the gene product is given in the brackets, if the full name does not already have a clear indication. In the genotypes, "T" stands for the transgene; "+" stands for a wild-type allele, "-" stands for a loss-of-function allele (presumed null); "flox" stands for the floxed allele; "lz" stands for the *LacZ* knock-in allele (usually a null allele for the endogenous gene). SM: Smooth muscle. SMC: Smooth muscle cell. UB: Ureteric bud. MM: Metanephric mesenchyme. VUR: Vesicoureteral reflux. UTO: Urinary tract obstruction. This is intended to be a representative list, instead of a complete list, both for animal models and for humans. This is especially true for cases with UTO as a minor component of a syndrome.

Genes/Mutations	New gene names, Gene full names, & [Function]	Alleles and the corresponding urinary defects	Proposed or likely Mechanism	Ref
Ace	*Angiotensin converting enzyme*	*Ace*$^{-/-}$ mice: hydronephrosis, renal parenchymal atrophy.	Defective pyeloureteral peristalsis as a result of a ureter differentiation defect, a urine concentration defect/polyuria, or both.	(60)
Adamts-1	*A disintegrin-like &metallopeptidase with thrombospondin type 1 motif, 1*	*Adamts-1*$^{-/-}$ mice: UPJ obstruction, hydronephrosis, hydroureter, other urogenital defects.	Unclear. Excessive collagen deposit was found at UPJ.	(72)
Agt	Angiotensinogen	*Agt*$^{-/-}$ mice: hydronephrosis, renal parenchymal atrophy.	Defective pyeloureteral peristalsis.	(61,62)
Agtr1a/b	*Angiotensin II receptor, type 1 (1a & 1b)*	*Agtr1*$^{-/-}$ *(1a & 1b)* mice: partial penetrance, hydronephrosis in older mutants, renal parenchymal atrophy.	Urinary SMC developmental Defect, renal pelvis development.	(58,59)
Agtr2	*Angiotensin II receptor, type 2*	*Agtr2*$^{-/-}$ mice: limited incidence of hydronephrosis, megaureter, renal parenchymal atrophy.	Ectopic and duplicated UB.	(56,57)
Aldh1a2	*Aldehyde dehydrogenase family 1 member A2* [encodes Raldh2, an enzyme in retinoic acid synthesis]	*Aldh1a2*$^{-/-}$ mice rescued by maternal retinoic acid: hydroureter & hydronephrosis	Defects in ureter maturation, especially the insertion of the ureter into the bladder.	(39)
Aqp2	*Aquaporin 2* [Water channel]	The *cph* mutants (*Aqp2*$^{S256L/S256L}$) have polyuria and hydronephrosis. Other *Aqp2* mutations also cause renal damage resembling obstructive nephropathy.	Polyuria overwhelms the pyeloureteral peristaltic machinery.	(70,73,74)
β-catenin	Same as *Ctnnb1* [adherens junction protein, involved in Wnt signaling]	*Hoxb7-Cre*$^{T/+}$*; β-catenin* $^{flox/flox}$ mice: hydroureter & hydronephrosis.	Ectopic and supernumerary UB.	(37)
Bmp4	*Bone morphogenetic protein 4*	*Bmp4*$^{+/-}$ mice: hydronephrosis, hydroureter, other urinary tract defects.	Ectopic and supernumerary UB.	(33,34)
Bmp5	*Bone morphogenetic protein 5*	*short ear* (*Bmp5*$^{-/-}$) mice: Hydroureter & hydronephrosis.	Spatial constraints in the lower abdominal cavity affect urinary transfer.	(75,76)

Genes/Mutations	New gene names, Gene full names, & [Function]	Alleles and the corresponding urinary defects	Proposed or likely Mechanism	Ref
Calcineurin	Same as *Ppp3c, protein phosphatase 3*. [serine/ threonine Protein phosphatase]	The *Pax3-Cre*$^{T/+}$; *Cnb1*$^{flox/flox}$ mice (with Calcineurin inactivation in the metanephric and ureteral mesenchyme): early postnatal hydronephrosis & hydroureter.	Pyeloureteral peristaltic defect, defect in urinary tract SMC development.	(4)
Dlgh1	Same as *Dlg1, Disk-large homolog 1* [scaffolding protein]	*Dlgh1*$^{-/-}$ mice: prenatal hydronephrosis, short ureter, and defects in the ureteral insertion into the bladder.	SM differentiation defect, ectopic UB.	(43,44)
Fcgr2b & Pdcd1	*Fc receptor, IgG, low affinity IIb & Programmed cell death 1* [cell surface membrane protein of the immunoglobulin superfamily]	Some *Fcgr2b*$^{-/-}$;*Pdcd1*$^{-/-}$ mice: hydronephrosis.	Autoimmune against UPKIIIa.	(66)
Fgfr2	*Fibroblast growth factor receptor 2*	Some *Pax3-Cre*$^{T/+}$; *Fgfr2*$^{flox/flox}$ mice have hydroureter.	Supernumerary UB, abnormal ureter connection	(28)
Foxc1/c2	*Forkhead box protein C1/C2* [transcription factor]	*Foxc1*$^{-/-}$ & *Foxc1*$^{+/-}$,*Foxc2*$^{+/-}$ mice: duplex kidney, ureter duplication, hydroureter, hydronephrosis.	Ectopic and supernumerary UB.	(77)
Gata2	*GATA binding protein 2* [transcription factor]	*Gata2*$^{-/-}$ mice (with YAC rescue of hematopoietic defects): hydroureter, hydronephrosis.	Unclear.	(78)
Hoxa13 & Hoxd13	*Homeobox A13* and *D13* [transcription factor]	*Hoxa13*$^{+/-}$; *Hoxd13*$^{-/-}$ mice: UVJ obstruction, hydronephrosis, hydroureter, other urogenital defects.	Patterning defects. May have homeotic transformation.	(79)
Hspa4l	*Heat shock protein 4 like* [chaperone?]	Some *Hspa4l*$^{-/-}$ mice have genetic background-dependent hydronephrosis.	Unclear.	(80)
Id2	*Inhibitor of DNA binding 2*	*Id2*$^{-/-}$ and *Id2*$^{+/-}$ mice have hydronephrosis.	UPJ development.	(81)
Il-9	*Interleukin 9*	Overexpressing *Il-9* by its own promoter in mice: hydronephrosis	Likely autoanitibodies against urinary tract components.	(67)
L1cam	*L1 cell adhesion molecule*	*L1cam*$^{-/-}$ mice: hydroureter & hydronephrosis.	Ectopic UB.	(82)
Lim1	Same as *Lhx1 – Lim homeobox protein 1* [transcription factor]	*Hoxb7-Cre*$^{T/+}$; *Lim1*$^{lz/flox}$ mice (with *Lim1* deletion in the UB derivatives): hydroureter & hydronephrosis.	Ureter differentiation.	
Limp-2 (Lgp85)	Same as *Scarb2* [scavenger receptor]	*Limp-2*$^{-/-}$ mice: kidney and ureter duplication, UPJ obstruction, hydroureter, and hydronephrosis.	Ectopic and supernumerary UB.	(83)

Genes/Mutations	New gene names, Gene full names, & [Function]	Alleles and the corresponding urinary defects	Proposed or likely Mechanism	Ref
Lx (luxate)	Unknown	Some $Lx^{+/-}$ and $^{-/-}$ mice: hydroureter, hydronephrosis, horseshoe kidney.	Crossing vessels suspected (84). New results point to early metanephric patterning defects (Unpublished results from our laboratory).	(84)
Megabladder	Unknown	Mutants have hydronephrosis, hydronephrosis, megabladder	Bladder SM development.	(85)
Nfia	*Nuclear factor I/A* [*transcription factor*]	$Nfia^{+/-}$ and $Nfia^{-/-}$ mice: VUR, hydronephrosis & hydroureter. Human $NFIA^{+/-}$ patients have similar defects.	Abnormal development of the UPJ and UVJ.	(47)
Nkcc2	Same as *Slc12a1-solute carrier family 12, member 1* [Sodium-potassium-chloride cotransporter]	$Nkcc2^{-/-}$ mice: polyuria and hydronephrosis of varying severity.	Possibly by polyuria overwhelming the pyeloureteral peristaltic machinery.	(86)
Pax2	*Paired box gene 2* [transcription factor]	$Pax2^{1Neu/+}$ mice: VUR. Other human and mouse mutant alleles also cause VUR in addition to renal agenesis.	Delay in urinary tract maturation in the $Pax2^{1Neu/+}$ mice.	(45)
Rara/Rarb2	*Retinoic acid receptor, alpha/ retinoic acid receptor beta 2*	$Rara^{-/-};Rarb2^{-/-}$ mice have hydronephrosis, hydroureter, VUR.	Defective differentiation of the MM.	(63)
Renin	Same as *Ren1* [an enzyme in the rennin-angiotension system]	$Renin^{-/-}$ mice: hydronephrosis, renal parenchymal atrophy.	Possibly by polyuria. It is also possible that the mutation disrupts SM differentiation.	(87)
Ret	*Ret* proto-oncogene [Gdnf receptor]	$Ret^{-/-}$ mice: renal agenesis, hydronephrosis, hydroureter, VUR.	UB initiation defect, ureter maturation defect.	(36,88,89)
		Mice carrying Ret alleles with specific mutation of the keytyrosines: CAKUT.	Ectopic and supernumerary UB.	(29)
		Mice overexpressing *Ret* in UB: VUR.	Ureter maturation defect.	(90)
Robo2	*Roundabout homolog 2* [SLIT2 receptor]	$Robo2^{-/-}$ mice and human patients carrying *ROBO2* mutations/ variants have VUR.	Ectopic and supernumerary UB.	(24,91,92)
Romk	Same as *Kcnj1*, potassium inwardly-rectifying channel, subfamily J, member 1	$Romk^{-/-}$ mice: hydronephrosis, water and electrolyte balance problem.	Unclear.	(93)
Shh	*Sonic hedgehog* [secreted signaling molecule]	$Hoxb7\text{-}Cre^{T/+}$; $Shh^{flox/flox}$ mice ($Shh^{-/-}$ in UB derivatives): hydroureter & hydronephrosis.	Mesenchymal proliferation, SMC differentiation.	(52)
Slc7a9	*Solute carrier family 7 member 9* [cationic amino acid transporter]	$Slc7a9^{-/-}$ mice: cystine urolithiasis and hydroureter.	Urolithiasis blocks urine flow. Not strictly “congenital”.	(71)
Slit2	*Slit homolog 2* [ROBO2 ligand]	$Slit2^{-/-}$ mice: hydroureter and hydronephrosis.	Ectopic and supernumerary UB.	(24)

Genes/Mutations	**New gene names, Gene full names, & [Function]**	**Alleles and the corresponding urinary defects**	**Proposed or likely Mechanism**	**Ref**
Smad4	*MAD homolog 4* [Tgfβ signal transducer]	*Bmp7-Cre*$^{T/+}$; *Smad4*$^{flox/flox}$ mice: hydronephrosis,	Defective MM differentiation.	(94)
Spry1	*Sprouty homolog 1* [RTK/ERK antagonist]	*Spry1*$^{-/-}$ mice: hydroureter and hydronephrosis.	Ectopic and supernumerary UB.	(31)
Spry2	*Sprouty homolog 2* [RTK/ERK antagonist]	*Spry2*$^{-/-}$ mice: renal agenesis, Hydroureter and hydronephrosis.	Ectopic and supernumerary UB.	(95)
Tbx18	*T-box transcription factor 18*	*Tbx18*$^{-/-}$ mice: hydronephrosis, hydroureter, and short ureters.	Ureteral SM defects due to ureteric mesenchyme differentiation anomalies.	(42)
Tensin	Same as *Tns1* [actin-binding protein]	*Tensin*$^{-/-}$ mice: cystic and hydronephrotic kidney at a few months of age.	Unclear, cell-cell, cell matrix interaction?	(96)
Tshz3	*Teashirt zinc finger family member 3* [transcription factor]	*Tshz3*$^{-/-}$ mice: hydronephrosis and hydronephrosis.	Defects in ureteral SM differentiation.	(53)
UpkII	*Uroplakin II* [Glycolsylated Transmembrane protein]	*UpkII*$^{-/-}$ mice: hydronephrosis, hydroureter, VUR.	Urothelial hyperplasia may block the urinary path. Alternatively, the urothelium defects may affect SM development.	(63)
UpkIII	*Uroplakin III* [Glycolsylated Transmembrane protein]	*UpkIII*$^{-/-}$ mice: hydronephrosis, hydroureter, VUR.	Urothelial hyperplasia may block the urinary path. Alternatively, the urothelium defects may affect SM development.	(64)