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Review Article

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Wnt/β-Catenin Signaling and Congenital Abnormalities of Kidney and Urinary Tract

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Keywords
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Abstract
Background: Precise regulation of cell-cell communication is vital for cell survival and normal function during embryogenesis. The Wnt protein family, a highly conserved and extensively studied group, plays a crucial role in key cell-cell signaling events essential for development and regeneration. Congenital anomalies of the kidney and urinary tract (CAKUT) represent a leading cause of chronic kidney disease in children and young adults, and include a variety of birth abnormalities resulting from disrupted genitourinary tract development during embryonic development. The incidence and progression of CAKUT may be related to the Wnt signal transduction mechanism. ***Summary:*** This review provides a comprehensive overview of the classical Wnt signaling pathway's role in CAKUT, explores related molecular mechanisms and provides new targets and intervention methods for the future treatment of the disease. ***Key Messages:*** The Wnt signal is intricately engaged in a variety of differentiation processes throughout kidney development.

Introduction

The development of the urinary system involves intricate and multifaceted processes that are meticulously coordinated both spatially and temporally. In recent years, the rapid advancements in molecular biology research revealed the significant role of Wnt signaling components during urinary system development. Elevated expression of these components underscores the pivotal role of Wnt signaling in urinary system morphogenesis. Notably, disruption of Wnt expression has been connected to various human kidney diseases and developmental anomalies, including congenital anomalies of the kidney and urinary tract (CAKUT), cystic kidney disease, acute and chronic kidney disease (CKD), and renal carcinoma. This review provides a comprehensive examination of the expression, regulation, and function of classical Wnt/β-catenin signaling in CAKUT.

The Wnt/β-Catenin Signaling Pathway

The discovery of the *Int-1* gene by Nusse and Varmus in 1982 marked the inception of the Wnt/β-catenin signaling pathway [1]. Subsequently, the identification of the *Wingless*

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(*Wg*) gene as a homolog of *Int-1* in 1987 led to the term "Wnt gene [2]." Currently, the mammalian genome encompasses 19 Wnt proteins, forming a conserved signaling molecules family [3]. These cysteine-rich proteins, typically consisting of about 400 amino acids, feature an N-terminal signal peptide for secretion [4]. Wnt signaling pathways can be categorized into canonical Wnt/β-catenin and noncanonical Wnt pathways [5]. The canonical Wnt pathway primarily regulates cell survival, proliferation, and fate decisions, while the noncanonical Wnt pathway (planar cell polarity and Wnt/Ca^{2+} pathway) controls cell polarity and migration, forming an interconnected regulatory network. This review focuses predominantly on the canonical Wnt pathway.

Porcupine O-acyltransferase is an enzyme that palmitoylates immature Wnt proteins in the endoplasmic reticulum of Wnt-producing cells [6]. Wntless (WLS) or Evenness interrupted (Evi) is essential for lipid-modified Wnts to be secreted and transported to the cell surface via the Golgi apparatus after palmitoylation [7]. The mechanism of how extracellular Wnt signals is transmitted to target cells is still under investigation. Wnt proteins interact to transmembrane receptor proteins Frizzled (Fz) and low-density lipoprotein receptor-related protein on target cell surfaces, inducing cytoplasmic accumulation of β-catenin and activating downstream signaling cascades.

The extracellular signal, membrane, cytoplasmic, and nuclear segments make up the Wnt/β-catenin pathway. Extracellular signals, mediated by Wnt proteins, interact with cell membrane receptors Fz and lipoprotein receptor-related protein 5/6. The cytoplasmic segment includes Dishevelled (Dvl), glycogen synthase kinase-3β (GSK-3β), AXIN, adenomatous polyposis coli (APC), and β-catenin. T-cell-specific transcription factor/lymphoid enhancer-binding factor family members and β-catenin downstream target genes, such as *c-Myc* and *cyclin D1* are involved in the nuclear section [8]. In the absence of Wnt signaling, the β-catenin degradation pathway is active, leading to the transcriptional inhibition of Wnt signaling. Activation of the canonical Wnt pathway inhibits this degradation pathway, resulting in β-catenin accumulation in the cytoplasm and its translocation to the nucleus. Nuclear β-catenin associates with transcription factors like lymphoid enhancer-binding factor 1/T-cell-specific transcription factor to regulate gene transcription [5] (shown in Fig. 1).

Congenital Abnormalities of Kidney and Urinary Tract

CAKUT encompasses a group of developmental disorders characterized by abnormal anatomical structures in the urinary system [9]. The estimated prevalence of CAKUT ranging from 4 to 60 per 10,000 births [10, 11]. CAKUT constitutes 30%–50% of congenital malformations in children and contributes significantly to CKD, affecting 30–60% of children with CKD and leading as the primary cause in this age group's end-stage renal disease [12–14]. According to clinical manifestations, CAKUT can be divided into renal abnormalities (including renal agenesis, hypoplasia, dysplasia, and multicystic dysplasia, etc.), ureteral abnormalities (including megaureter, vesicoureteral reflux, and obstruction at the ureteropelvic junction, etc.), and bladder and urethral abnormalities (such as posterior urethral valve) [15, 16]. CAKUT has been further classified as non-syndromic or syndromic, with studies indicating that 34% of infants with urinary system congenital abnormalities exhibit malformations in other systems [17]. There are over 200 clinical syndromes including the CAKUT phenotype, including renal coloboma syndrome, branchiootorenal syndrome, diabetic syndrome, renal cysts, and Zaki syndrome [18, 19].

The pathogenesis of CAKUT stems from the disruption of normal nephrogenesis, influenced by environmental, genetic, and epigenetic factors. The formation of the mammalian kidney is a multistage process that involves interactions between different cell types and molecular pathways. The kidney grows through the phases of the pronephros, mesonephros, and metanephros after originates from the intermediate mesoderm. The metanephros, the permanent kidney, undergoes key stages of metanephrogenesis, including ureteric bud (UB) induction, mesenchymal-to-epithelial transition (MET), branching morphogenesis, and nephron patterning [10]. During development, the pronephros and mesonephros degenerate, and the metanephric kidney becomes the permanent kidney, crucial for hormone regulation and maintaining water and electrolyte balance [20]. The UB extends from the nephric duct, initiating branching and invasion of metanephric mesenchyme (MM), leading to nephron formation. This process involves mesenchymal-to-epithelial transition, progressing through condensed mesenchyme, renal vesicle formation, and the development of comma-shaped and S-shaped bodies, ultimately giving rise to mature kidney structures [21–24] (shown in Fig. 2).

Wnt Signaling and CAKUT

Considering the Wnt signaling pathway controls cellular functions including differentiation, proliferation, MET, tubulogenesis, and morphogenesis from the earliest

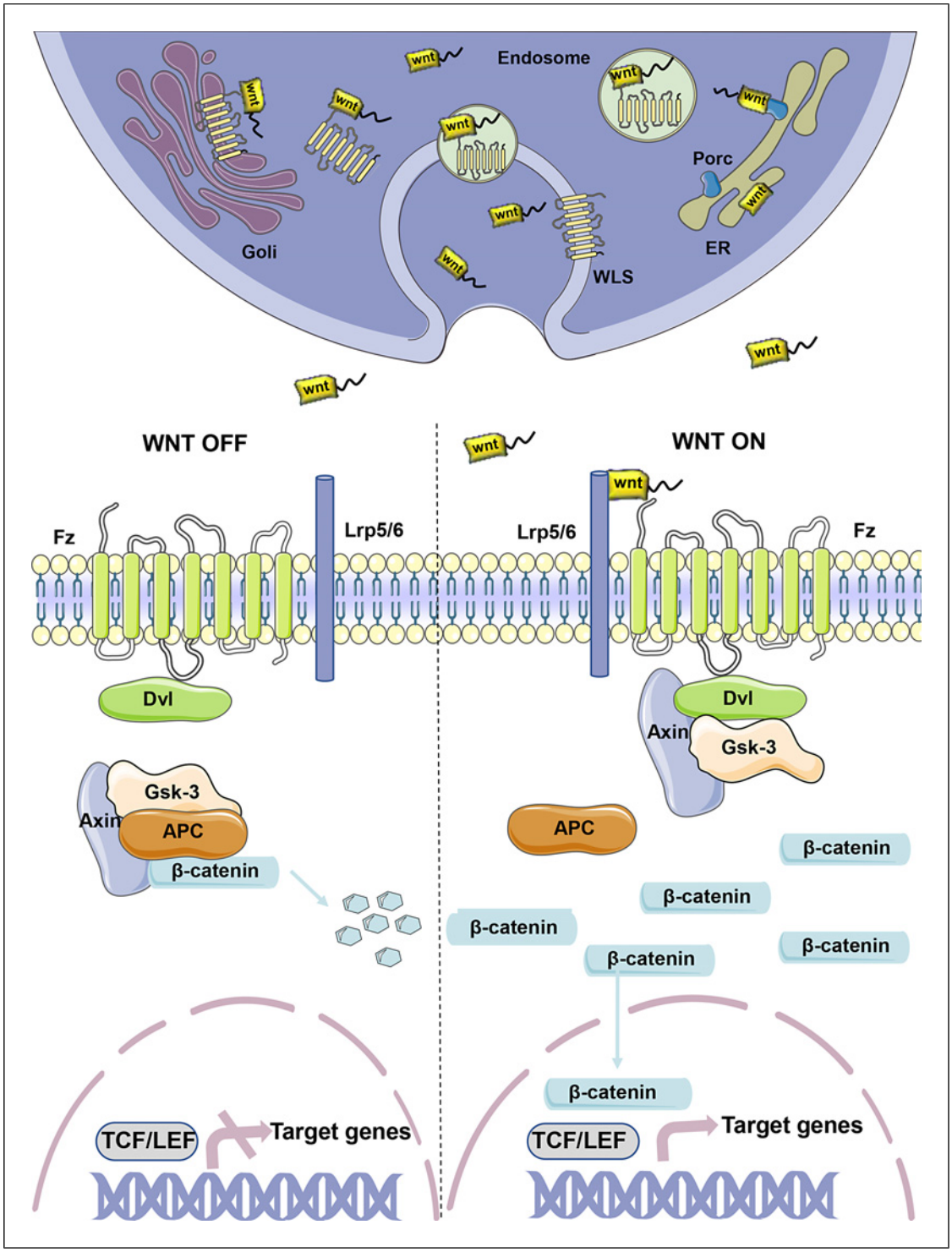

Fig. 1. Diagram describe the complexity of Wnt signal transduction starting from the processes involved in Wnt ligand biogenesis and secretion by Wnt-producing cells followed by a comprehensive overview of the molecular signaling events ultimately resulting in enhanced transcription of specific genes in Wnt receiving cells. Goli, Golgi apparatus; Porc, Porcupine O-acyltransferase; ER, endoplasmic reticulum; Fz, frizzled; LRP, lipoprotein receptor-related protein; Dvl, Dishevelled; Gsk-3, glycogen synthase kinase-3; APC, adenomatous polyposis coli. Modified from Nusse and Varmus [1].

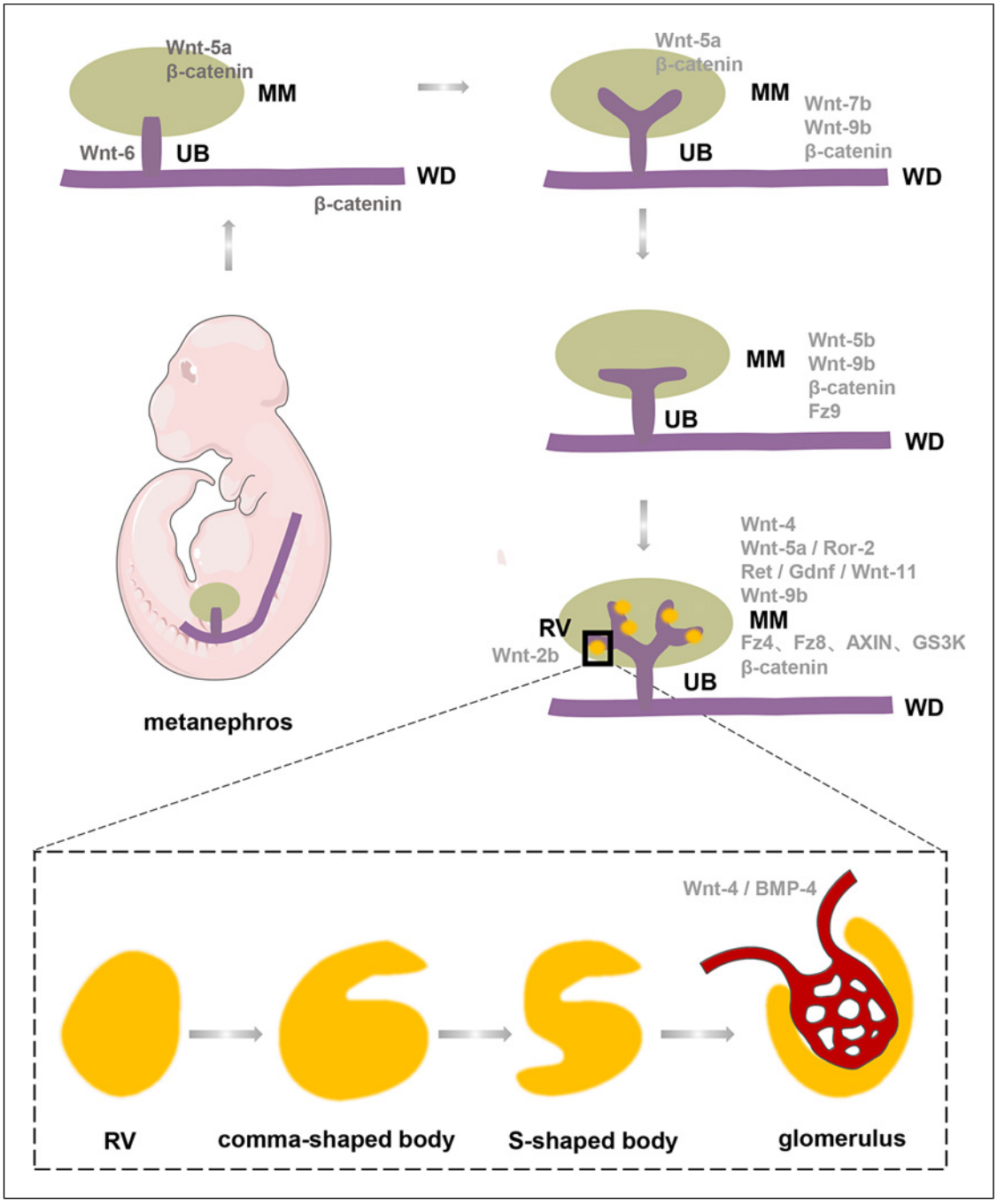

Fig. 2. Diagram depicts the major events in mammalian nephrogenesis. MM, metanephric mesenchyme; ND, nephric duct; UB, ureteric bud; WD, Wolffian ducts. Modified from Boivin et al. [25].

phases of embryogenesis, it is essential to kidney development. The subsequent section of this review explores the important relationship between CAKUT and Wnt signaling pathway components and their pathophysiological effects (shown in Tables 1, 2; Fig. 2).

Renal Abnormalities

Renal Agenesis, Hypoplasia, Dysplasia

Plenty of studies have highlighted the significant expression of various Wnt ligands during urinary system development, making them potential candidates for

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Table 1. Wnt components involved in kidney development

Wnt components	Developmental roles
Extracellular segment	
Wnt-2b	Stimulate ureter development
Wnt-3	Affects the development of the cloaca
Wnt-4	Initiate pronephric tubules development, MET, and the maturation of nephrons
Wnt-5a	Regulate IM extension and interaction between the MM and WD
Wnt-6	Induce kidney tubule development
Wnt-7b	Mediate the establishment of a cortico-medullary axis
Wnt-9b	Regulate differentiation, proliferation and condensation of mesenchyme cells, induce MET, stimulate renal tubule morphogenesis
Wnt-11	Regulate pronephric development, ureteric branching and nephron maturation
WLS	Unclear
Membrane segment	
Fz	Mediate UB growth and regeneration of new nephrons
LRP5/6	Disrupt the signaling network consisting of Ret cascades
Cytoplasmic segment	
DVL	Affect the development of renal cilia
GSK-3β	Affects epithelial differentiation and full segregation of nephrons
AXIN	Regulate the development of ureteral bud/collecting duct
APC	Affect renal development(unclear) and increase susceptibility to renal carcinoma
β-catenin	Regulate branching morphogenesis, urethral formation and nephrogenic progenitor cell population
Nuclear segment	
TCF/LEF	Unclear
c-Myc	May involve in the pathogenesis of PKD

LEF/TCF, lymphoid enhancer-binding factor 1/T-cell-specific transcription factor.

CAKUT diseases (shown in Table 2). While the pronephros is transiently expressed in mammals and then diminishes, it performs a crucial function in the larval stages of fish and amphibians Wnt-4 gene knockdown in Xenopus embryos led to the lack of pronephric tubules [26]. The current knowledge about the Fz receptor is scarce, only several Fz genes (such as Fz1, 3, 4, 7, 8, and 9) have been found to be localized in developing kidneys [27]. In Xenopus, inhibiting Xfz8 led to abnormalities in pronephric tubule branching and disrupted the tubules' and the pronephric duct's epithelial morphogenesis [28]. Some studies have discovered prominent Fz7 expression in the mesonephros, suggesting Fz7 is involved in epithelialization [29].

Previous research indicates that developing kidneys expressed Wnt-2b. To investigate the potential role of Wnt-2b in nephrogenesis, Lin et al. [30] detected the expression of Wnt-2b in perirenal mesenchymal cells. In vitro functional studies have shown that cells expressing Wnt-2b could stimulate ureteral development, but could not induce tubule formation [30].

Wnt-4 is initially expressed in pretubular mesenchymal cells and maintains its expression during kidney development [31]. Patients with Wnt-4 mutations are associated with renal defects and Müllerian-duct regression, highlighting the clinical relevance of this signaling pathway [32, 33]. Considering that, infer that Wnt-4 is essential for kidney development. To investigate this hypothesis, Stark et al. [34] utilized gene targeting technology in embryonic stem cells to produce mice lacking the *Wnt-4* gene. As expected, Wnt-$4^{-/-}$ mice did not survive beyond 24 h after birth and had small agenic kidneys composed of undifferentiated mesenchyme. This transformation of mesenchymal cells was found to be mediated by Wnt-4. And speculated that Wnt-4 may regulate mesenchymal aggregation through the modulation of cell adhesion factors, such as cadherins and integrins [34]. Subsequently, Kispert et al. [35] provided further proof that Wnt-4 functions as a significant autoregulator of the MET. Wnt-4 signaling also governs the fate of smooth muscle cells by activating the *Bmp-4* gene. The absence of smooth muscle cell differentiation results in a secondary deficit in the renal vessels' maturation as well as an accompanying shortage in the pericytes surrounding the growing vessels [36].

Table 2. Wnt components in animal models and human urinary system phenotypes

Wnt components	Animal model	Human urinary system phenotype
Extracellular segment		
Wnt-2b	N/A	N/A
Wnt-3	Wnt-3$^{-/-}$ mice cannot develop mesoderm, knockdown of Wnt-3 in zebrafish resulted in cloaca malformations	Tetra-amelia syndrome ? (OMIM# 273395)
Wnt-4	Wnt-4$^{-/-}$ mice die shortly after birth, Müller duct regression and renal dysgenesis	SERKAL syndrome ?(OMIM# 611812)
Wnt-5a	Wnt-5a$^{-/-}$ mice led to CAKUT, Wnt-5a knockdown in zebrafish caused glomerular cysts and renal tubule dilation	Robinow syndrome (OMIM#180700)
Wnt-6	N/A	N/A
Wnt-7b	Wnt-7b$^{-/-}$ mice resulted in the absence of the renal medulla	N/A
Wnt-9b	Wnt-9b $^{-/-}$ mice died within 24 h of birth and displayed vestigial kidneys,Wnt-9b$^{-/flox}$ mice develop cystic kidneys	Bilateral renal agenesis?
Wnt-11	Wnt-11$^{-/-}$ mice disrupt UB branching and lead to a decreased number of glomeruli	N/A
WLS	Knock-in mice carrying WLS mutations exhibited cystic medullary hydronephrosis	Zaki syndrome(OMIM#619648)
Membrane segment		
Fz	Fz4 and Fz8 double knockout mice observed UB growth and kidney size defects	N/A
LRP5/6	Lrp$^{-/-}$ resulted in hypoplastic and/or cystic kidneys	N/A
Cytoplasmic segment		
DVL	N/A	Robinow syndrome (OMIM#616331)
GSK-3β	N/A	N/A
AXIN	N/A	N/A
APC	Conditional deletion of Apc in mice leads to the presence of numerous kidney cysts	N/A
β-catenin	Conditional deletion or overexpression of β-catenin causes various renal defects	N/A
Nuclear segment		
TCF/LEF	N/A	N/A
c-Myc	N/A	N/A

N/A, not applicable; ?, indicates that the relationship between the phenotype and gene is provisional.

Nishita et al. [37] proposed that Wnt-5a deficient mice exhibited dysregulation in the positioning and proliferation of MM cells, resulting in spatial and temporal aberrations in the interaction between MM and WD. This led to inappropriate GDNF signaling in the WD. Their findings indicated that the Wnt-5a signaling pathway plays a indispensable role in regulating MM morphogenesis. Some researchers have proposed the participation of Wnt-5a in orchestrating UB development. It promotes the formation of the basement membrane and organization of collective duct epithelial cells, which are essential for kidney-collecting duct patterning [38].

Wnt-6 exhibits early stage expression in UB and cell lines expressing Wnt-6 have the capacity to induce tubulogenesis in vitro. The expression of Wnt-6 stimulates the interaction between epithelial and mesenchymal tissues while also governing mesenchymal development, thereby promoting the formation of kidney tubules [39, 40].

Wnt-9b is abundantly expressed in the cells of the WD epithelium and later in the UB stalk [41]. Mouse embryos deficient in Wnt-9b can develop to term but typically die away 24 h after birth. Histological analysis reveals an absence of intermediate precursor stages, ultimately resulting in a lack of nephrons and the presence of some rudimentary epithelia. Recent research by Lemire et al. [42] reported 4 patients with bilateral renal agenesis hypoplasia who had homozygous Wnt-9b mutations

from two independent families, thereby establishing a link between Wnt-9b and renal defects in humans. Prior research has demonstrated the active role of Wnt-9b signaling in progenitor cells, with progenitor cells failing to expand in Wnt-9b mutants. Using Lyso-tracker, Karner et al. [43] discovered that the wild-type mesenchymal cells exhibited a proliferation rate approximately five times higher than that of Wnt-9b mutants. These results imply that Wnt-9b may regulate mesenchymal cell differentiation and proliferation. Wnt-9b acts upstream of Wnt-4 and is recognized as the initial inducer of MET in urogenital system development. The paracrine action of Wnt-9b induces the expression of Wnt-4, Pax8, and Fgf8 in the ventral CM. As mentioned earlier, these genes play a role in the nephrogenesis process. Therefore, it is not surprising that Wnt-9b is crucial for the initial induction from the UB to the CM and the condensation of mesenchymal cells [25, 44, 45].

Genetic and experimental evidence from previous studies establishes the essential role of Wnt-11 in mediating convergent extension movements during zebrafish gastrulation [46]. The *Wnt-11* gene is distinctly identified at the tips of the UB epithelium, indicating a potential role in regulating ureteric branching events. All Wnt-11 deficient mice did not survive beyond 2 days post-partum. Newborn Wnt-11$^{-/-}$ mice exhibited normal nephron organization, although the glomeruli number was nearly halved compared to the wild-type. The small kidney size may be attributed to defective ureteric branching morphogenesis. It has been demonstrated that the ureteric epithelial branching process heavily depends on the Ret/Gdnf pathway. Interestingly, Gdnf expression is diminished in Wnt-11$^{-/-}$ mice kidneys, and conversely, Wnt-11 expression is significantly reduced in Ret/Gdnf mutants. Recent image-based modeling indicates that the dense packing of ureteric tips is facilitated by the positive feedback loop between Wnt-11 and Gdnf [47]. Hence, ureteric branching morphogenesis is regulated by the interaction of Wnt-11 and Ret/Gdnf signals within a regulatory circuit [48]. In Wnt-11 mutants, nephron progenitor differentiation was accelerated, polarized distribution was disrupted, and the early depletion of the nephron progenitor pool occurred. Nephron progenitors were shown to lose stable attachments to the tips of the ureters when Wnt-11 is absent by live imaging [49]. All of these factors contribute to defects and malformations in nephron maturation.

Distinct spatial and temporal patterns of β-catenin expression observed during kidney development underscore the tight regulatory control of this protein throughout the developmental process. β-catenin exhibits expression in key regions, including the ureteric epithelium, MM, and various stages of developing nephrons [25]. Previous investigations have revealed the essential role of Gata3 in initiating normal ureteric budding. Loss of β-catenin specifically in the WD causes a simultaneous decrease in Gata3 expression and, remarkably, ectopic ureter budding [50]. Furthermore, targeted knockout of β-catenin within ureteric epithelial cells results in reduced expression of transcription factors like Emx2. Strikingly, mice deficient in Emx2 and those lacking β-catenin manifest analogous phenotypes, characterized by renal agenesis and ureteral branching defects. This strongly supports the hypothesis that β-catenin governs Emx2 expression, thereby regulating branching morphogenesis [51]. Moreover, overexpression β-catenin has been observed in the tissues of individuals with renal dysplasia, suggesting its potential involvement in the disease's pathogenesis [52]. Recent research conducted by Xue et al. [53] has revealed that overexpression of lncRNA 4933425B07Rik (Rik) may inhibit the Wnt/β-catenin signaling, resulting in a cascade of CAKUT phenotypes, primarily characterized by renal hypoplasia. Mice models with directed overexpression of β-catenin in the ureteric epithelium display significant abnormalities in nephrogenesis and branching morphogenesis [54]. When β-catenin is deleted from the kidney's condensed mesenchyme, its target genes are reducing expression, resulting in a decreased nephrogenic progenitor cell population [55].

In the mouse, the reduction of kidney size and UB growth defects seen in the Fz4 and Fz8 knockout mouse models is similar to the phenotypes seen in mouse models deficient in Wnt-11, suggesting Fz4 and Fz8 may cooperate to transduce the Wnt-11 signal. Additionally, it showed striking functional redundancy among several Fz receptors, just like Wnt ligands [56]. In zebrafish, the Fz9b mutation decreased the total number of kidney nephrons, resulted in tubule morphological defects, and inhibited the regeneration of new nephrons after injury [57]. Axin2 shows elevated expression at the branching tips of the UB while being expressed at lower levels in the stalk. This implies that Axin2 likely plays a crucial role in the development of the ureteral bud and collecting duct [58]. The application of GSK-3 inhibitors in isolated kidney mesenchymes, led to complete nephron segregation and extensive epithelial differentiation, indicating the significant role of GSK-3 during the initial phases of nephrogenesis [59].

A critical stage in the secretion of all Wnt ligands is the transportation of Wnt from the Golgi apparatus to the cell membrane, which is carried out by WLS [60]. Several studies have demonstrated that WLS mutations affect convergent extension processes, similar to Wnt-11 [61].

The reciprocal regulation between Wnt and WLS is vital for embryonic axis formation and organogenesis [62]. Zaki syndrome is characterized by a pleiotropic multiorgan condition. WLS is the only genetic factor known to cause this disorder. WLS knock-in mouse embryos exhibit a variety of developmental defects, including evident cystic medullary hydronephrosis [19]. Our research group previously reported a case of *WLS* gene compound heterozygous mutation (p.Tyr476Cys and p.Arg139Cys) causing right renal hypoplasia in children [63]. However, the exact relationship between the WLS protein and kidney development disorders remains unclear. It is likely that the WLS protein affects the concentration of Wnt ligands transported to the cell membrane, which in turn may lead to associated phenotypes.

Polycystic Kidney Disease

Wnt-9b$^{-/flox}$ mice develop cystic kidneys, indicating a later function for Wnt-9b in renal tubule development. Cyst formation arises from abnormalities in planar cell polarity, which relies on noncanonical Wnt signaling via Wnt-9b [43]. Insufficient or excessive levels of β-catenin can results in the onset and progression of diseases and also assume a dual function in polycystic kidney disease (PKD), where either the loss or gain of its activity contributes to the progression of the disease [64].

Renal tissues from both animal models of PKD and PKD patients exhibit elevated c-Myc expression. This observation implies that the increased expression of c-Myc might have a crucial role in the development of PKD [58]. Previous studies have shown that Dvl affects the development of renal cilia by impacting the noncanonical Wnt/PCP signaling pathway. Aberrant expression and distribution of Dvl protein can eventually lead to cystic kidney disease [65].

Prior research has reported that targeted removal of the APC in the renal epithelium of mice results in neonatal mortality, with subsequent histological examination revealing the presence of numerous kidney cysts. Moreover, the absence of APC not only leads to the development of multiple dysplastic foci but also significantly heightens the susceptibility to renal carcinoma. This dual impact on both structural integrity and the risk of malignancy highlights the far-reaching implications of APC in renal health [66, 67].

Ureteral Abnormalities

Duplex Ubs

Wnt-5a expression during the process of nephrogenesis follows specific temporal patterns, with successive expressions in IM, MM, and WD/UB epithelium [41]. In zebrafish, glomerular cysts developed and renal tubules dilated as a result of Wnt-5a knockdown. Global Wnt-5a knockout in mice produced pleiotropic kidney abnormalities, including hydronephrosis, agenesis, fused kidney, and duplex kidney/ureter [68]. One receptor or co-receptor for Wnt-5a has been discovered as Ror2, a member of the receptor tyrosine kinase family [69]. In an initial study, the *Ror2* gene was reported to cause Robinow syndrome, which is characterized by skeletal abnormalities [70]. Interestingly, several renal diseases, such as duplex kidney/ureter and kidney agenesis, have been observed in relation to Robinow syndrome [71]. Subsequently, Yun et al. [72] delved into exploring the role of the Wnt-5a/Ror2 signaling in kidney and made significant breakthroughs. Duplex Ubs were produced by conditional ablation of Wnt-5a in the mesoderm at E7.5, suggesting that Wnt-5a aided in the formation of IM prior to the appearance of the metanephros. When one copy of Wnt-5a was additionally deleted in Ror2 homozygous mutant mice, the incidence of duplex collecting systems significantly increased. These results imply that the dysgenesis of IM extension may be a mechanism by which the Wnt-5a/Ror2 signaling pathway contributes to the development of duplex kidneys [72].

Aberrant Ureter-Bladder Link

Recently, some scholars have suggested that Wnt-7b can be a candidate gene for clinical manifestations such as bladder ureteral reflux [73]. Some research indicates that an aberrant ureter-bladder link is the cause of the renal medulla's absence in Wnt-5a-deficient kidneys [74].

Bladder and Urethral Abnormalities

Bladder Exstrophy

Bladder exstrophy is a rare disease, occurring in around 1 out of every 30,000 live births [75]. Niemann et al. [76] looked into a family whose four affected fetuses had urogenital and craniofacial abnormalities as well as autosomal recessive tetra-amelia. Finding a Wnt-3 mutation (Q83X) in tetra-amelia suggests that Wnt-3 is crucial in the development of human limbs and the craniofacial and urogenital regions. Mice with a knockout of the *Wnt-3* gene exhibit an inability to develop mesoderm during their embryonic development. Knockdown of *Wnt-3* in zebrafish resulted in expansion of the cloaca lumen and disorganization of the cloaca epithelium [77]. Moreover, a highly conserved 32 kb intergenic region between Wnt-3 and Wnt-9b has been identified by a genome-wide association analysis as a possible susceptibility locus for bladder exstrophy [78].

Co-seeding mesenchymal stem cells (MSCs) with donor-matched $CD34^+$ hematopoietic stem cells/progenitor cells has shown synergistic enhancing effects on various facets of bladder tissue. The results observed with Wnt-5a overexpressing MSCs closely align with those previously reported in the co-transplantation of $CD34^+$ hematopoietic stem cells/progenitor cells with MSCs, highlighting Wnt-5a as a potentially crucial factor in tissue regeneration following bladder dilation [79].

Urethral Abnormalities

Exposure to exogenous estrogen or environmental endocrine disruptors can cause hypospadias or masculinization by interfering with the genetic regulation of the Wnt-4, 5a, 7a, and 9a pathways during development [80].The present findings also suggest that the Wnt ligand receptor Fz1 exhibits selective expression in the urethral epithelium, implying that it may have particular functions in the urethral epithelium's early development [81]. Knocking out β-*catenin* in the mesenchyme and ectoderm cells can cause severe hypospadias [82].

Discussion

In the study of CAKUT, we recognize the complexity of its pathogenic mechanisms, involving developmental signaling pathways, genetic factors (gene mutations, copy number variations), and environmental factors (such as poor diet, maternal diseases, placental dysfunction, and drug intake). Over 50 genes are linked to CAKUT in humans, with HNF1β and PAX2 being the most common pathogenic genes, accounting for 5% to 15% of all CAKUT patients. Multiple signaling pathways, including Wnt, BMP, and GDNF/Ret, regulate urinary system development. Disruptions in these pathways and their interactions can lead to congenital anomalies in CAKUT [83]. Therefore, the genetic association discovered in CAKUT may suggest therapeutic development strategies, and gene therapy and stem cell transplantation are promising treatment methods for hereditary kidney disease. The diagnosis of CAKUT predominantly depends on conventional imaging methods including urinary system ultrasound, urography and nuclear imaging. Contemporary researchers suggest the next phase should incorporate whole-genome sequencing into standard diagnostic procedures. The meticulous integration of whole-genome sequencing data with comprehensive omics information, epigenetics, encompassing gene expression, proteomics, and metabolomics, along with detailed environmental and clinical data, is crucial. This integrated approach aims to distinguish between benign variants and infrequent deleterious ones, prioritizing and categorizing them appropriately. There are also emerging biomarkers available to assess early kidney damage, such as the PAX2 protein, the urine EGF/urine MCP1 ratio and the 98-peptide signature in amniotic fluid [84–86]. Unfortunately, the therapies for CAKUT are mostly limited to symptom management; there is not an definitive cure at currently. If the disease worsens further, renal replacement therapy is necessary, among which kidney transplantation is the most fundamental treatment method for children with end-stage renal disease. Therefore, early prevention and diagnosis of CAKUT are crucial. In the early stages of pregnancy, it is essential to implement comprehensive protective measures for pregnant women, along with actively pursuing scientific and reasonable prenatal interventions.

The development of a functional kidney relies on precise coordination among various signaling molecules, with the Wnt pathway playing a pivotal role. This pathway is crucial not only in kidney development but also in conditions like acute kidney injury, CKD, and renal cancer. While significant alterations in gene expression have been identified in individuals with CAKUT, the precise molecular mechanisms of the disorder remain incompletely understood. In both human and murine CAKUT models, researchers have observed aberrant expression of transcription factors, signaling pathways, and numerous growth factors (Table 2). Recent years have witnessed significant advancements in this field, including the identification of new targets in the Wnt signaling and a clearer understanding of its underlying mechanisms. Notably, there is a growing repertoire of small molecule Wnt agonists and inhibitors that hold promise for modulating this signaling pathway, potentially transforming it into an effective therapeutic approach for various kidney disorders. Emerging research findings indicate that drug interventions might also hold potential for addressing structural birth defects arising from Wnt signaling pathway abnormalities during pregnancy. For instance, the administration of a Wnt agonist (CHIR99021) has shown promise in partially restoring embryonic development, and 4-Phenylbutyric acid (4-PBA) can rescue the decreased mutant WLS expression in vitro, opening up exciting possibilities for future therapeutic strategies.

In conclusion, over the past two decades, the concerted application of cutting-edge gene screening technologies, microarray analyses, and the development of animal gene

knockout/knock-in models has yielded significant insights into the pivotal roles of specific molecules and signaling pathways in urinary system development. The findings stemming from this body of research may serve as a crucial experimental and theoretical foundation for pioneering clinical strategies aimed at the treatment and prevention of CAKUT. The integration of key embryonic kidney development signals into molecular diagnostic approaches for renal dysplasia and hereditary nephropathy represents an important frontier in this field. Such efforts may further advance the prospects for renal repair and regeneration in cases of kidney damage. However, it is essential to acknowledge that our journey in this domain is far from complete, and numerous fundamental questions remain unanswered. Chief among these is the exploration of the noncanonical Wnt signaling pathway's influence on urinary system development and its specific interplay with the canonical signaling pathway. These questions represent fertile ground for future research and may uncover new avenues for advancing our understanding of kidney development and its associated pathologies.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization: B.Z. and G.D.; writing – original draft preparation: C.Y. and L.Z.; writing – review and editing: A.Z. and Z.J.; project administration: G.D. All authors have read and agreed to the published version of the manuscript.

References

1 Nusse R, Varmus HE. Many tumors induced by the mouse mammary tumor virus contain a provirus integrated in the same region of the host genome. Cell. 1982;31(1):99–109. https://doi.org/10.1016/0092-8674(82)90409-3

2 Rijsewijk F, Schuermann M, Wagenaar E, Parren P, Weigel D, Nusse R. The Drosophila homology of the mouse mammary oncogene int-1 is identical to the segment polarity gene wingless. Cell. 1987;50(4):649–57. https://doi.org/10.1016/0092-8674(87)90038-9

3 Kusserow A, Pang K, Sturm C, Hrouda M, Lentfer J, Schmidt HA, et al. Unexpected complexity of the Wnt gene family in a sea anemone. Nature. 2005;433(7022):156–60. https://doi.org/10.1038/nature03158

4 MacDonald BT, Tamai K, He X. Wnt/β-Catenin signaling: components, mechanisms, and diseases. Developmental Cell. 2009;17(1):9–26. https://doi.org/10.1016/j.devcel.2009.06.016

5 Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004;20(1):781–810. https://doi.org/10.1146/annurev.cellbio.20.010403.113126

6 Nile AH, Hannoush RN. Fatty acylation of Wnt proteins. Nat Chem Biol. 2016;12(2):60–9. https://doi.org/10.1038/nchembio.2005

7 Bartscherer K, Pelte N, Ingelfinger D, Boutros M. Secretion of wnt ligands requires evi, a conserved transmembrane protein. Cell. 2006;125(3):523–33. https://doi.org/10.1016/j.cell.2006.04.009

8 Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, et al. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther. 2022;7(1):3. https://doi.org/10.1038/s41392-021-00762-6

9 Sanna-Cherchi S, Westland R, Ghiggeri GM, Gharavi AG. Genetic basis of human congenital anomalies of the kidney and urinary tract. J Clin Invest. 2018;128(1):4–15. https://doi.org/10.1172/jci95300

10 Nicolaou N, Renkema KY, Bongers EMHF, Giles RH, Knoers NVAM. Genetic, environmental, and epigenetic factors involved in CAKUT. Nat Rev Nephrol. 2015;11(12):720–31. https://doi.org/10.1038/nrneph.2015.140

11 Tain Y-L, Luh H, Lin C-Y, Hsu C-N. Incidence and risks of congenital anomalies of kidney and urinary tract in newborns: a population-based case-control study in taiwan. Medicine. 2016;95(5):e2659. https://doi.org/10.1097/md.0000000000002659

12 Zheng Q, Furth SL, Tasian GE, Fan Y. Computer aided diagnosis of congenital abnormalities of the kidney and urinary tract in children based on ultrasound imaging data by integrating texture image features and deep transfer learning image features. J Pediatr Urol. 2019;15(1):75.e1–7. https://doi.org/10.1016/j.jpurol.2018.10.020

13 Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27(3):363–73. https://doi.org/10.1007/s00467-011-1939-1

14 Westland R, Renkema KY, Knoers NVAM. Clinical integration of genome diagnostics for congenital anomalies of the kidney and urinary tract. Clin J Am Soc Nephrol. 2020;16(1):128–37. https://doi.org/10.2215/cjn.14661119

15 Spinder N, Bergman JEH, van Tongeren M, Boezen HM, Kromhout H, de Walle HEK. Maternal occupational exposure to endocrine-disrupting chemicals and urogenital anomalies in the offspring. Hum Reprod. 2021;37(1):142–51. https://doi.org/10.1093/humrep/deab205

16 Kumar BH, Krishnamurthy S, Chandrasekaran V, Jindal B, Ananthakrishnan R. Clinical spectrum of congenital anomalies of kidney and urinary tract in children. Indian Pediatr. 2019;56(7):566–70. https://doi.org/10.1007/s13312-019-1556-9

17 Stoll C, Dott B, Alembik Y, Roth M-P. Associated nonurinary congenital anomalies among infants with congenital anomalies of kidney and urinary tract (CAKUT). Eur J Med Genet. 2014;57(7):322–8. https://doi.org/10.1016/j.ejmg.2014.04.014

18 Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta. Nephrol Dial Transpl. 2004;19:2703–8.

19 Guoliang C, Emmanuelle S-R, Changuk C, Zhen L, Wang L, Khatoo M, et al. A human pleiotropic multiorgan condition caused by deficient wnt secretion. The New Engl J Med N Engl J. 30:385.
20 Capone VP, Morello W, Taroni F, Montini G. Genetics of congenital anomalies of the kidney and urinary tract: the current state of play. Int J Mol Sci. 2017;18(4):E796. https://doi.org/10.3390/ijms18040796
21 Toka HR, Toka O, Hariri A, Nguyen HT. Congenital anomalies of kidney and urinary tract. Semin Nephrol. 2010;30(4):374–86. https://doi.org/10.1016/j.semnephrol.2010.06.004
22 Seely JC. A brief review of kidney development, maturation, developmental abnormalities, and drug toxicity: juvenile animal relevancy. J Toxicol Pathol. 2017;30(2):125–33. https://doi.org/10.1293/tox.2017-0006
23 Schedl A. Renal abnormalities and their developmental origin. Genetics. 2007;12.
24 Talati AN, Webster CM, Vora NL. Prenatal genetic considerations of congenital anomalies of the kidney and urinary tract (CAKUT). Prenat Diagn. 2019;39(9):679–92. https://doi.org/10.1002/pd.5536
25 Boivin FJ, Sarin S, Lim J, Javidan A, Svajger B, Khalili H, et al. Stromally expressed β-catenin modulates Wnt9b signaling in the ureteric epithelium. PLoS One. 2015;10(3):e0120347. https://doi.org/10.1371/journal.pone.0120347
26 Saulnier DME, Ghanbari H, Brändli AW. Essential function of Wnt-4 for tubulogenesis in the Xenopus pronephric kidney. Dev Biol. 2002;248(1):13–28. https://doi.org/10.1006/dbio.2002.0712
27 McMahon AP, Aronow BJ, Davidson DR, Davies JA, Gaido KW, Grimmond S, et al. GUDMAP: the genitourinary developmental molecular anatomy project. J Am Soc Nephrol. 2008;19(4):667–71. https://doi.org/10.1681/asn.2007101078
28 Satow R, Chan T, Asashima M. The role of Xenopus frizzled-8 in pronephric development. Biochem Biophys Res Commun. 2004;321(2):487–94. https://doi.org/10.1016/j.bbrc.2004.06.166
29 Beaton H, Andrews D, Parsons M, Murphy M, Gaffney A, Kavanagh D, et al. Wnt6 regulates epithelial cell differentiation and is dysregulated in renal fibrosis. Am J Physiol Ren Physiol. 2016;311(1):F35–45. https://doi.org/10.1152/ajprenal.00136.2016
30 Lin Y, Liu A, Zhang S, Ruusunen T, Kreidberg JA, Peltoketo H, et al. Induction of ureter branching as a response to Wnt-2b signaling during early kidney organogenesis. Dev Dyn. 2001;222(1):26–39. https://doi.org/10.1002/dvdy.1164
31 Mugford JW, Yu J, Kobayashi A, McMahon AP. High-resolution gene expression analysis of the developing mouse kidney defines novel cellular compartments within the nephron progenitor population. Dev Biol. 2009;333(2):312–23. https://doi.org/10.1016/j.ydbio.2009.06.043
32 Lauber AB, Konrad D, Navratil N, Schoenle EJ. A WNT4 mutation associated with Müllerian-duct regression and virilization in a 46 XX woman. The New Engl J Med. 351(8):792–8. https://doi.org/10.1056/NEJMoa040533
33 Mandel H, Shemer R, Borochowitz ZU, Okopnik M, Knopf C, Indelman M, et al. SERKAL syndrome: an autosomal-recessive disorder caused by a loss-of-function mutation in WNT4. Am J Hum Genet. 82(1):39–48.https://doi.org/10.1016/j.ajhg.2007.08.005.
34 Stark K, Vainio S, Vassileva G, McMahon AP. Epithelial transformation of metanephric mesenchyme in the developing kidney regulated by Wnt-4. Nat Nature. 1994:15:372.
35 Kispert A, Vainio S, McMahon AP. Wnt-4 is a mesenchymal signal for epithelial transformation of metanephric mesenchyme in the developing kidney. Development. 1998;125(21):4225–34. https://doi.org/10.1242/dev.125.21.4225
36 Itäranta P, Chi L, Seppänen T, Niku M, Tuukkanen J, Peltoketo H, et al. Wnt-4 signaling is involved in the control of smooth muscle cell fate via Bmp-4 in the medullary stroma of the developing kidney. Developmental Biol. 2006;11.
37 Nishita M, Qiao S, Miyamoto M, Okinaka Y, Yamada M, Hashimoto R, et al. Role of Wnt5a-Ror2 signaling in morphogenesis of the metanephric mesenchyme during ureteric budding. Mol Cell Biol. 2014;34(16):3096–105. https://doi.org/10.1128/mcb.00491-14
38 Pietilä I, Prunskaite-Hyyryläinen R, Kaisto S, Tika E. Wnt5a deficiency leads to anomalies in ureteric tree development, tubular epithelial cell organization and basement membrane integrity pointing to a role in kidney collecting duct patterning. PLoS One. 2016;15.
39 Itäranta P, Lin Y, Peräsaari J, Roël G, Destrée O, Vainio S. Wnt-6 is expressed in the ureter bud and induces kidney tubule development in vitro. Genesis. 2002;32(4):259–68. https://doi.org/10.1002/gene.10079
40 Wei M, Zhang C, Tian Y, Du X, Wang Q, Zhao H. Expression and function of WNT6: from development to disease. Front Cell Dev Biol. 2020;8:558155. https://doi.org/10.3389/fcell.2020.558155
41 Meng P, Zhu M, Ling X, Zhou L. Wnt signaling in kidney: the initiator or terminator? J Mol Med. 2020;98(11):1511–23. https://doi.org/10.1007/s00109-020-01978-9
42 Lemire G, Zheng B, Ediae GU, Zou R, Bhola PT, Chisholm C, et al. Homozygous *WNT9B* variants in two families with bilateral renal agenesis/hypoplasia/dysplasia. Am J Med Genet. 2021;185(10):3005–11. https://doi.org/10.1002/ajmg.a.62398
43 Karner CM, Chirumamilla R, Aoki S, Igarashi P, Wallingford JB, Carroll TJ. Wnt9b signaling regulates planar cell polarity and kidney tubule morphogenesis. Nat Genet. 2009;41(7):793–9. https://doi.org/10.1038/ng.400
44 Carroll TJ, Park J-S, Hayashi S, Majumdar A, McMahon AP. Wnt9b plays a central role in the regulation of mesenchymal to epithelial transitions underlying organogenesis of the mammalian urogenital system. Developmental Cell. 2005;9(2):283–92. https://doi.org/10.1016/j.devcel.2005.05.016
45 Halt K, Vainio S. Coordination of kidney organogenesis by Wnt signaling. Pediatr Nephrol. 2014;29(4):737–44. https://doi.org/10.1007/s00467-013-2733-z
46 Heisenberg CP, Tada M, Rauch GJ, Saúde L, Concha ML, Geisler R, et al. Silberblick/Wnt11 mediates convergent extension movements during zebrafish gastrulation. Nature. 2000;405(6782):76–81. https://doi.org/10.1038/35011068
47 Menshykau D, Michos O, Lang C, Conrad L, McMahon AP, Iber D. Image-based modeling of kidney branching morphogenesis reveals GDNF-RET based Turing-type mechanism and pattern-modulating WNT11 feedback. Nat Commun. 2019;10(1):239. https://doi.org/10.1038/s41467-018-08212-8
48 Majumdar A, Vainio S, Kispert A, McMahon J, McMahon AP. Wnt11 and Ret/Gdnf pathways cooperate in regulating ureteric branching during metanephric kidney development. Development. 2003;130(14):3175–85. https://doi.org/10.1242/dev.00520
49 O'Brien LL, Combes AN, Short KM, Lindström NO, Whitney PH, Cullen-McEwen LA, et al. Wnt11 directs nephron progenitor polarity and motile behavior ultimately determining nephron endowment. Elife. 2018;7:e40392. https://doi.org/10.7554/elife.40392
50 Grote D, Boualia SK, Souabni A, Merkel C, Chi X, Costantini F, et al. Gata3 acts downstream of β-catenin signaling to prevent ectopic metanephric kidney induction. PLoS Genet. 2008;4(12):e1000316. https://doi.org/10.1371/journal.pgen.1000316
51 Miyamoto N, Yoshida M, Kuratani S, Matsuo I, Aizawa S. Defects of urogenital development in mice lacking Emx2. Development. 1997;124(9):1653–64. https://doi.org/10.1242/dev.124.9.1653
52 Sarin S, Boivin F, Li A, Lim J, Svajger B, Rosenblum ND, et al. β-Catenin overexpression in the metanephric mesenchyme leads to renal dysplasia genesis via cell-autonomous and non–cell-autonomous mechanisms. Am J Pathol. 2014;184(5):1395–410. https://doi.org/10.1016/j.ajpath.2014.01.018
53 Xue S, Du X, Yu M, Ju H, Tan L, Li Y, et al. Overexpression of long noncoding RNA 4933425B07Rik leads to renal hypoplasia by inactivating Wnt/β-catenin signaling pathway. Front Cell Dev Biol. 2023;11:1267440. https://doi.org/10.3389/fcell.2023.1267440
54 Bridgewater D, Di Giovanni V, Cain JE, Cox B, Jakobson M, Sainio K, et al. β-Catenin causes renal dysplasia via upregulation of Tgfβ2 and Dkk1. J Am Soc Nephrol. 2011;22(4):718–31. https://doi.org/10.1681/asn.2010050562

55 Boivin FJ, Bridgewater D. β-Catenin in stromal progenitors controls medullary stromal development. Am J Physiol Ren Physiol. 2018;314(6):F1177–87. https://doi.org/10.1152/ajprenal.00282.2017
56 Ye X, Wang Y, Rattner A, Nathans J. Genetic mosaic analysis reveals a major role for frizzled 4 and frizzled 8 in controlling ureteric growth in the developing kidney. Development. 2011;138(6):1161–72. https://doi.org/10.1242/dev.057620
57 Kamei CN, Gallegos TF, Liu Y, Hukriede N, Drummond IA. Wnt signaling mediates new nephron formation during zebrafish kidney regeneration. Development. 2019;146(8):dev168294. https://doi.org/10.1242/dev.168294
58 Merkel CE, Karner CM, Carroll TJ. Molecular regulation of kidney development: is the answer blowing in the Wnt? Pediatr Nephrol. 2007;22(11):1825–38. https://doi.org/10.1007/s00467-007-0504-4
59 Kuure S, Popsueva A, Jakobson M, Sainio K, Sariola H. Glycogen synthase kinase-3 inactivation and stabilization of β-catenin induce nephron differentiation in isolated mouse and rat kidney mesenchymes. J Am Soc Nephrol. 2007;18(4):1130–9. https://doi.org/10.1681/asn.2006111206
60 Nygaard R, Yu J, Kim J, Ross DR, Parisi G, Clarke OB, et al. Structural basis of WLS/Evi-mediated wnt transport and secretion. Cell. 2021;184(1):194–206.e14. https://doi.org/10.1016/j.cell.2020.11.038
61 Rochard L, Monica SD, Ling ITC, Kong Y, Roberson S, Harland R, et al. Roles of Wnt pathway genes wls, wnt9a, wnt5b, frzb and gpc4 in regulating convergent-extension during zebrafish palate morphogenesis. Development. 2016;143:2541–7.
62 Fu J, Jiang M, Mirando AJ, Yu H-MI, Hsu W. Reciprocal regulation of Wnt and Gpr177/mouse Wntless is required for embryonic axis formation. Proc Natl Acad Sci U S A. 2009;106(44):18598–603. https://doi.org/10.1073/pnas.0904894106
63 Yu C, Wang C, Zhou W, Zhang A, Jia Z, Zheng B, et al. Compound heterozygous variants in WLS gene causes Zaki syndrome. Clin Genet. 2023;104(2):226–9. https://doi.org/10.1111/cge.14334
64 Conduit SE, Hakim S, Feeney SJ, Ooms LM, Dyson JM, Abud HE, et al. β-catenin ablation exacerbates polycystic kidney disease progression. Hum Mol Genet. 2019;28:230–44.
65 Goggolidou P. Wnt and planar cell polarity signaling in cystic renal disease. Organogenesis. 2014;10(1):86–95. https://doi.org/10.4161/org.26766
66 Qian C-N, Knol J, Igarashi P, Lin F, Zylstra U, Teh BT, et al. Cystic renal neoplasia following conditional inactivation of apc in mouse renal tubular epithelium. J Biol Chem. 2005;280(5):3938–45. https://doi.org/10.1074/jbc.m410697200
67 Sansom OJ, Griffiths DFR, Reed KR, Winton DJ, Clarke AR. Apc deficiency predisposes to renal carcinoma in the mouse. Oncogene. 2005;24(55):8205–10. https://doi.org/10.1038/sj.onc.1208956
68 Huang L, Xiao A, Choi SY, Kan Q, Zhou W, Chacon-Heszele MF, et al. Wnt5a is necessary for normal kidney development in zebrafish and mice. Nephron Exp Nephrol. 2014;128(1–2):80–8. https://doi.org/10.1159/000368411
69 Nishita M, Itsukushima S, Nomachi A, Endo M, Wang Z, Inaba D, et al. Ror2/frizzled complex mediates Wnt5a-induced AP-1 activation by regulating Dishevelled polymerization. Mol Cell Biol. 2010;30(14):3610–9. https://doi.org/10.1128/mcb.00177-10
70 Afzal AR, Rajab A, Fenske CD, Oldridge M, Elanko N, Ternes-Pereira E, et al. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of ROR2. Nat Genet. 2000;25(4):419–22. https://doi.org/10.1038/78107
71 Tufan F, Cefle K, Türkmen S, Türkmen A, Zorba U, Dursun M, et al. Clinical and molecular characterization of two adults with autosomal recessive Robinow syndrome. Am J Med Genet. 2005;136A(2):185–9. https://doi.org/10.1002/ajmg.a.30785
72 Yun K, Ajima R, Sharma N, Costantini F, Mackem S, Lewandoski M, et al. Non-canonical Wnt5a/Ror2 signaling regulates kidney morphogenesis by controlling intermediate mesoderm extension. Hum Mol Genet. 2014;23(25):6807–14. https://doi.org/10.1093/hmg/ddu397
73 McCoy MD, Sarasua SM, DeLuca JM, Davis S, Phelan K, Rogers RC, et al. State of the science for kidney disorders in phelan-McDermid syndrome: UPK3A, FBLN1, WNT7B, and CELSR1 as candidate genes. Genes. 2022;13(6):1042. https://doi.org/10.3390/genes13061042
74 Yun K, Perantoni AO. Hydronephrosis in the Wnt5a-ablated kidney is caused by an abnormal ureter-bladder connection. Differentiation. 2017;94:1–7. https://doi.org/10.1016/j.diff.2016.11.006
75 Margiana R, Juwita W, Ima K, Faizah Z, Supardi S. Analyzing the factors that contribute to the development of embryological classical type of bladder exstrophy. Anat Cell Biol. 2023;56(4):421–7. https://doi.org/10.5115/acb.23.056
76 Niemann S, Zhao C, Pascu F, Stahl U, Aulepp U, Niswander L, et al. Homozygous WNT3 mutation causes tetra-amelia in a large consanguineous family. The Am J Hum Genet. 2004;74(3):558–63. https://doi.org/10.1086/382196
77 Liu P, Wakamiya M, Shea MJ, Albrecht U, Behringer RR, Bradley A. Requirement for Wnt3 in vertebrate axis formation. Nat Genet. 1999;22(4):361–5. https://doi.org/10.1038/11932
78 Reutter H, Draaken M, Pennimpede T, Wittler L, Brockschmidt FF, Ebert A-K, et al. Genome-wide association study and mouse expression data identify a highly conserved 32 kb intergenic region between WNT3 and WNT9b as possible susceptibility locus for isolated classic exstrophy of the bladder. Hum Mol Genet. 2014;23(20):5536–44. https://doi.org/10.1093/hmg/ddu259
79 Snow-Lisy DC, Diaz EC, Bury MI, Fuller NJ, Hannick JH, Ahmad N, et al. The role of genetically modified mesenchymal stem cells in urinary bladder regeneration. PLoS One. 2015;10(9):e0138643. https://doi.org/10.1371/journal.pone.0138643
80 Chen Y, Yu H, Pask AJ, Fujiyama A, Suzuki Y, Sugano S, et al. Hormone-responsive genes in the SHH and WNT/β-catenin signaling pathways influence urethral closure and phallus growth†. Biol Reprod. 2018;99:806–16. https://doi.org/10.1093/biolre/ioy117
81 Li J, Willingham E, Baskin LS. Gene expression profiles in mouse urethral development. BJU Int. 2006;98(4):880–5. https://doi.org/10.1111/j.1464-410x.2006.06435.x
82 Bouty A, Ayers KL, Pask A, Heloury Y, Sinclair AH. The genetic and environmental factors underlying hypospadias. Sex Dev. 2015;9(5):239–59. https://doi.org/10.1159/000441988
83 Kohl S, Habbig S, Weber LT, Liebau MC. Molecular causes of congenital anomalies of the kidney and urinary tract (CAKUT). Mol Cell Pediatr. 2021;8(1):2. https://doi.org/10.1186/s40348-021-00112-0
84 Zheng Y, Xu J, Guo W, Xu H, Chen J, Shen Q, et al. The significance of Pax2 expression in the ureter epithelium of children with vesicoureteric reflux. Hum Pathol. 2015;46(7):963–70. https://doi.org/10.1016/j.humpath.2015.01.007
85 Bartoli F, Penza R, Aceto G, Niglio F, D'Addato O, Pastore V, et al. Urinary epidermal growth factor, monocyte chemotactic protein-1, and β2-microglobulin in children with ureteropelvic junction obstruction. J Pediatr Surg. 2011;46(3):530–6. https://doi.org/10.1016/j.jpedsurg.2010.07.057
86 Klein J, Buffin-Meyer B, Boizard F, Moussaoui N, Lescat O, Breuil B, et al. Amniotic fluid peptides predict postnatal kidney survival in developmental kidney disease. Kidney Int. 2021;99(3):737–49. https://doi.org/10.1016/j.kint.2020.06.043