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Mini Review

Duplex Kidney Formation

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ABSTRACT

Background: The CAKUT-congenital abnormalities of kidneys and urinary tract are various groups of conditions which, jointly are among those foremost abnormalities that are found in newly born children. CAKUTs are produced via way of means of mutations in an exceptionally massive quantity of genes that showcase a huge variety of symptoms, which is consistent with their variety. The vast bulk of duplex irregularities is asymptomatic and has no therapeutic potential. However, such kidneys having double ureter can cause problems.

Methodology: Early identification of these malformations in the patients is crucial since serious problems are noticeable and can be adequately dealt with early management. A duplex aggregation system is that the most typical malformation of the tract and reflux is the most common abnormality related to it.

Result: The vast majority of asymptomatic kidney duplications are discovered by chance and appear to be misdiagnosed as kidney which is normally functioning with whole or incomplete duplication. Though the association between urinary tract infection, vesicoureteral reflux, and parenchymal scarring during a non-duplicated collecting system is standard, very little has been written regarding the prevalence and distribution of vesicoureteral reflux and parenchymal scarring in duplicated systems. Induction of the ureter, reviews genes which are considered not only as hazardous factors in the development of renal duplexes but also discusses the molecular and cellular mechanisms that might give rise to such kind of mutation.

Conclusion: In this review, we will be concentrating on double ureter kidneys, which is a common type of CAKUT which is symptomless still makes prone to hydronephrosis and vesicoureteric reflux.

Keywords: CAKUT; Malformation; Vesicoureteric reflux; Hydronephrosis

INTRODUCTION

This system is very complex and is created by over forty different types of cells whose development has to proceed in very extremely union pattern. The tract is composed of a pair of ureters and kidneys, urethra and bladder which portrays the most expelling system of organisms. It is not stunning that variations in natural process genes will beget a huge diversity of malformations those are generally sorted to be non-inheritable malformations of the urinary tract and the kidney. The flaws in kidney are ranging from nephritic non development (insufficient development of the excretory organ itself) to dysplasia (decreased size), abnormally (abnormal development of tissue), terminal differentiation defects and cystic dysplasia. Reflux (VUR), anomaly (beginning of channel in bottom aspect of penis), and posterior canal valves are all lower tract anomalies that always create outflow blockages. Though individual deformities are considered rare disorders, CAKUT as a whole has cases of three to six new babies out of a thousand born affected, making it one of the most common anomalies found in new-born children. Although anureteropelvic junction obstruction (UPJO) and duplicated accumulating system and do not appear to be uncommon site defects in paediatric urology, they do occur together infrequently, accounting for 2–7% of upper tract malformations [1,2]. The proportion of duplication is partial, with the ureters converging above the ureteral opening at a certain unspecified period in the future. In contrast to complete duplication defects, those frequently source signs or affect kidney function, certain types of duplication hardly generate medical concerns [3]. Incomplete duplication can make surgical rectification problematic since the lower and upper pole ureters integrate proximally, along with pyelopyelostomy or pyeloureterostomy needs to be carefully picked out [4]. Age of patients, febrile tract infection (UTI) incidences, decrease or higher pole positioning, certainly duplication is partial or entire, function of renal unit, and operator's choice are all factors that influence management [5]. There are no high-quality methods of control or procedures

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to ensure. Instead, we'll focus on double (or duplex) kidneys, a prevalent subtype of CAKUT that is usually ignored in the studies.

Urinary system development

It's important to understand how the urinary device functions in order to learn the aetiology of double ureter containing kidneys. The cloacal endoderm gives rise to two parts urethra and bladder whereas the intermediate mesoderm (IM) gives rise to both kidneys and ureters [6]. The urogenital tract is made up of independent germ layers. As a result, urinary system malformations could be grouped as upper and lower tract congenital abnormalities (CALUT is a common abbreviation for the latter). Despite this physiological divergence, some writers include ureter anomalies as a component of lower gastrointestinal tract congenital disorders. The anterior (dorsal) pole of the IM has nephric duct initiates the kidney formation process in mammals. As development proceeds, the ND's epithelial cells multiply and actively advance towards the direction of the nephrogenic cord's caudal limit [7-9]. A series of tubules grow inside the nephrogenic cord as the ND develops caudally, allowing the ND to connect to the cloaca via a mechanism involving GATA3 and LHX1, RET, along with retinoic acid and FGF signalling [10,11]. The much more anteriorly located pronephric tubules in mammals have been regarded evolutionary residues which serve no purpose. Following that, a surge of mesonephric tubules broadens and forms groups. Tubules located further caudally do not drain into the ND and are hence non-functional; however, the ND related to the rostral tubules act as an embryonic kidney [12,13]. Pronephros and mesonephros are two temporary systems found inside the mammalian embryos that either perishes (pronephrons) and otherwise change (mesonephrons) as the embryo develops. In animals, the metanephrons are the perpetual kidneys that arise on the IM's most caudal aspect. Metanephrons are first recognised as a population of constrained mesenchymal cells inside the nephrogenic cords which exhibit a specific type of microsatellites (SIX2, HOX11, EYA1 and GDNF) [13,14]. The creation and expansion of a solitary ureteric bud from the ND that can infiltrate the MM and undergo a biased dichotomous splitting process, is induced by communicating from the metanephric mesenchyme (MM) in regular improvement (ureter of T shape). The renal duct system (ureteric system) records similar budding cycles, which typically contain tri-tips but ultimately lead to ureter branching [15]. The ureter's signals, on the other hand, cause the MM to discriminate between kidney's functioning devices which are nephrons. We encourage the reader to the most recent reviews for similar information during this technique [16,17]. The development of the urinary system also isn't limited to renal development; this even encompasses substantial lower tract physiological remodelling. The common nephric duct [CND], also known as the distal section of ND, connects the developing UB here to cloaca at first. Once the urorectal septum grows down, a cloaca is separated into the urogenital sinus and anorectal sinus which are ventrally and dorsally positions respectively [6,18,19]. The urethra will be shaped by the posterior component of the cranial urogenital sinus, which will stretch to extend further into bladder. Apoptosis destroys the CND while progress advances, resulting in the ureter's eventual merger with the bladder and the formation of the ureterovesical junction [20].

Classification and epidemiology

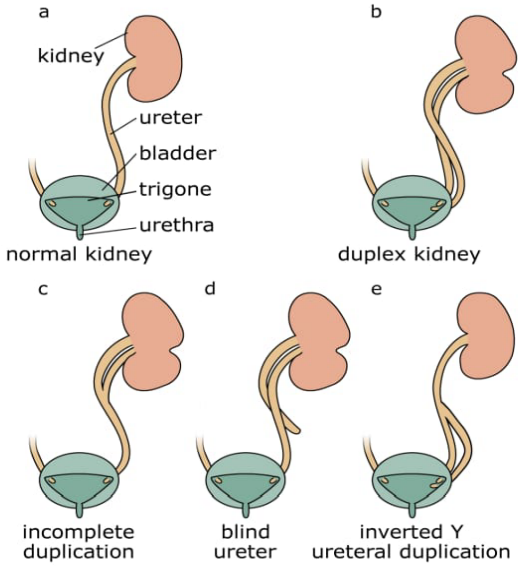
Multiple class structures have been proposed to characterise this ailment since duplex structures can have a variety of phenotypes (Figure 1) [21]. Similar ureteral opening in bladder is occupied by both the poles in kidneys with partial duplication. Prior reaching ampulla there is a splitting of ureter of a single UB whereas, ureter rises completely in those double ureter containing kidneys that have bifid pelvis. That's most anticipated outcome of a premature first branching event. When UBs develop from the nephritic duct, whole duplications are significantly more common. The lowering pole of the kidney is often regular, whereas the top pole is irregular, a differentiation defined mostly by idea that such ectopic ureteric budding develops anteriorly to the regular ureteric budding that causes top pole of such kidneys with double ureters to develop [22,23]. Two or more ureteral orifices drain from a single normal kidney in the inverted Y-ureteral duplication. The merging of separate UBs immediately before or while they approach the anlagen of kidney is hypothesised to generate inverted Y-ureteral duplication [24]. An extremely rare H-shaped ureter has even been observed [25]. The first genuine initiation steps of the ureter can be traced all the way back to the aetiology of maximum duplex kidneys. An extra UB appears as rostral enlargement towards the main protrusion in the great majority of cases. The elevated (abnormal) kidney pole, on the other hand, empties into the bladder at a site distant to the decreasing kidney pole's opening in adulthood [26]. The Weigert–Meyer rule, which describes the large amount of remodelling that occurs at some point during development on the future ureter–bladder junction, is a confusing phenomenon. The ureter penetrates into the forming bladder and travels upwards as apoptosis eliminates the CND (Figure 1) [6,27–29].

Molecular pathways that control ureter induction

The GDNF/RET signalling axis is a crucial mechanism governing this technique, and interactions between the MM as well as ND are obliged to implement the development of ureter [30]. The MM expresses GDNF, a distant member of the reworking increase element beta (TGF) subfamily of chemical messengers, while its corresponding receptor RET is present throughout the ND. The co-receptor GFR1 aids GDNF binding to RET. The importance of those genes throughout ureter expansion was already demonstrated utilising gene targeted on in, and homozygous alterations in both genes resulted in ureter inducing failures and, as a result, renal agenesis. When GDNF binds to receptor tyrosine kinase RET, it auto phosphorylates and selects the tyrosine phosphatase SHP2 [31,32], which catalyses the conversion of several intracellular pathways, including PLCγ/Ca2+, RAS/MAPK and PI3K-AKT [33], and regulates the expression of a number of downstream goal genes [34]. Cell motility and proliferation are both induced by activated RET signalling. Experiments with chimeric cells have shown that exotic cells flow closer to the UB's end, while Ret variant cells remain stuck behind. Under normal circumstances, this cell sorting mechanism ensures a strong and directed reaction those results in the outgrowth of a particular ureteric budding on one side.

Factors that regulate GDNF expression

GDNF activation mostly in mesenchyme is mediated by a set of transcriptional regulators, including EYA1, SALL1 and PAX2. Loss of ureteric induction and, as a result, renal agenesis comes from the



Group	Genotype	Mechanism	Reference
GDNF domain			
	Robo2$^{-/-}$	Abnormal *Gdnf* expression domain MM fails to separate from WD	Grieshammer *et al.*[64] Wainwright *et al.*[63]
	Slit2$^{-/-}$	Abnormal *Gdnf* expression domain	Grieshammer *et al.*[64]
	Foxc1$^{-/-}$	MM fails to reduce in size	Kume *et al.*[65] Komaki *et al.*[66]
	Sox11$^{-/-}$	MM fails to reduce in size	Neirijnck *et al.*[66]
Increased sensitivity of WD			
	Bmp4$^{+/-}$	Lack of inhibition of WNT11, a target of GDNF	Miyazaki *et al.*[79] Michos *et al.*[81]
	Ift25$^{-/-}$, *Ift27*$^{-/-}$	Increased sensitivity of WD through Gremlin-BMP4 cascade	Desai *et al.*[84]
	Gli3$^{\Delta 699/\Delta 699}$	Increased sensitivity of WD through Gremlin-BMP4 cascade	Blake *et al.*[85]
	Agtr2$^{-/Y}$	Disrupted renin-angiotensin signalling leads to aberrant UB morphogenesis	Nishimura *et al.*[91] Yosypiv *et al.*[90]
	p53$^{-/-}$, *p53*$^{tg/-/-}$	Increased response of WD to GDNF signal. Two ureters fuse in the later development and resemble a bifurcation	Saifudeen *et al.*[97] El-dahr *et al.*[98]
	Fat4$^{-/-}$ *Fjx1*$^{-/-}$	Premature branching with incomplete duplication due to overactive GDNF-RET signalling	Saburi *et al.*[94] Zhang *et al.*[95]
	Hoxb7-Cre β-*catenin*$^{ex3/+}$	Ectopic activation of UB branching pathway in WD	Marose *et al.*[74]
	Spry1$^{-/-}$	Increased sensitivity of WD to GDNF-RET signalling	Basson *et al.*[89]
	Gata3ND$^{-/-}$	The entire length on WD is covered by ectopic UBs, most of which subsequently regress	Grote *et al.*[75]
Cell polarity defect			
	T-Cre Wnt5af$^{fl/\Delta}$	Double UB, abnormal morphology of posterior WD, defects in IM morphogenesis	Yun *et al.*[99]
	Ror2$^{-/-}$	Similar to *Wnt5a* phenotype	Yun *et al.*[99]
Cell adhesion defect			
	L1$^{-/Y}$	Either incomplete or complete duplication. Double UB on WD or accessory budding from the main ureter	Debiec *et al.*[100]
Unknown			
	Pax2$^{+/-}$	Premature branching with incomplete duplication, linked with inactivation of GDNF expression	Brophy *et al.*[101]
	Pax2-Cre Lim1$^{fl/\Delta}$	WD fails to extend caudally; UB is absent or Y-shaped	Pedersen *et al.*[9]
	Cc2d2a, Mks1, Cep290, Dync2h1, Tbc1d32, Tmem67	Duplex kidney as a part of a ciliopathy phenotype	San agustin *et al.*[96]
	Sox17$^{Y259N/+}$	Duplicated pyeloureteral collecting system	Gimelli *et al.*[76]
	Nfia$^{-/-}$	Partial ureteral duplication	Lu *et al.*[102]
	Adamts18$^{-/-}$	Complete ureteral duplication, increased nephron endowment	Rutledge *et al.*[103]

Figure 1: Anatomy of the duplex kidney is classified. (a) Compared to a normal kidney, (b) Kidney showing dual poles and ureters is result of complete duplication, (c) A Y-shaped ureter results from incomplete duplication, (d) The ureters which are dismantled do not empty into the bladder & (e) 2 ureters combine before reaching the kidney in the unusual occurrence of inverted Y-ureteral duplication.

in ND have a distinct response to local boom elements (FGF and GDNF), as well as premature cellular proliferation and different cell adhesion qualities. Consequently, cells with adequate RET and GATA3 tiers separate from GATA3-deficient cells then grow, creating aberrant kidneys and buds [37]. A versatile protein Beta-catenin, associated with cell adhesion and transcriptional control, appears to become one of the variables impacting this increase. Depending on -catenin inactivation with in ND triggers a series of abnormalities in kidney, including development of kidneys with double ureters [38]. The transcription elements SOX9 and EMX2, both of which are thought to be involved in ureter budding, were impaired in these variants [39]. Ectopic rising, on the other hand, was seen most commonly observed in cases where a mosaic was caused by deficiency of β-catenin expression.

B-catenin decrease due to oxygen deprivation has also been associated to duplex kidneys in a number of CAKUT traits [40]. The transcription factor GATA370 is at least partially responsible for β-catenin movement during renal development. SOX17 variants were discovered in a group of CAKUT patients who had a replicated pyeloureteral apparatus, among other symptoms. The researchers have found that the variant altered protein equilibrium and reduction in β-catenin activities [41]. As a result, it's possible that the mutant SOX17 protein causes a reduction in β-catenin, GATA3 tiers have been reduced as a result. LHX1 (LIM1) appears to be as important as GATA3 in permitting regular sprouting [42]. In ND analogues, tissue-specific elimination of LIM1 causes renal hypoplasia, hydronephrosis, and ND extending impairment. Certain Lim1 provisional variants also have partial kidney ureter duplication, before entering the bladder, every pole of kidney merges. The earliest UB splitting activity was traced back to this form of duplex kidney, which has a Y-shaped instead of a T-shaped structure due to poor UB documentation. A series of direct inhibition that block the RET signalling pathways seem to be in place to control ureter expansion to a centralized location. In addition, BMP signalling tends being an inhibitor of ureter growth and splitting and CAKUT anomalies are caused by polymorphic Bmp4 variants, which include kidneys with such deformities [43]. FGF and BMP signals are shown to inhibit lung epithelial splitting as well as kidney development [44]. RET and FGF receptors are tyrosine kinases (receptors that bind to a specific tyrosine) having intracellular signalling pathways that are similar, we can deduce that BMP's adversarial movement has an equivalent effect on RET transmission. MM cells target the BMP regulator Gremlin (Grem1), which inhibits BMP action and allows ureter development, particularly at the region of the future renal [45]. Human CAKUT sufferers have both been found to have heterozygous BMP4 and GREM1 mutations, though it's not always obvious whether these genes' variants also lead to duplex kidney development [46]. A number of genes associated in kidney malformation development appear to regulate the BMP/Gremlin axis. Duplex kidney development was 50% penetrance in variants for the intraflagellar carrier proteins IFT27 or IFT25, that are likely to enhance GLI3R, a regulator of SHH signalling [47]. CAKUT is generated by the constitutive expression of Gli3 (Gli3699), a truncation mutation that is common in Pallister–Hall syndrome and is thought to render tissue more receptive to SHH signalling [48]. The trait has been linked to increased ND sensitivity through decreased BMP4 signalling. Several cilia-related genes have also been connected to the development of duplex kidneys [49]. SHH regulation is intricately related to the number one cilia, which is a crucial part of the cell in cellular signalling [50]. Because SHH signalling has been connected to the formation of duplex kidneys, it's tempting to think that the cilia-associated genes listed earlier play a role in this process as well. Cytoplasmic antagonists, in combination with extracellular enhancers, can be used to prevent ureter development. In the absence of GDNF, Sprouty (Spry1) inhibits MAPK signalling, resulting in the creation of numerous UBs [51]. Angiotensin receptor signalling appears to be important not just in reducing Spry1 but also in boosting Ret expression, and Agtr2 has several CAKUT characteristics, including a duplex system [52,53]. There have been no harmful SPRY1 mutations found in CAKUT patients to date, and it's unknown how much this gene plays a role in the development of duplex kidneys in humans. Surprisingly, in the absence of Spry1, ureter induction does not require GDNF signalling. As a result, FGF signalling could be thought of as a reinforcing cue that promotes epithelial development and budding. We wish to emphasize that GDNF/RET transmission has replaced FGF in the branching of kidney epithelial cells. FGF signalling is a major factor in the branching morphogenesis of several organs, including the lung. Finally, there are treatments for specific tissues. The loss of Fat4 in the nephrogenic cord results in a duplex kidney phenotype, which can be restored by lowering the GDNF dosage (GDNF+/-). The formation of duplex kidneys has been connected to a variety of genes, but the molecular pathways that lead to supernumerary buds remain unknown. Because the pathogenic aspect of alterations for duplex kidney development is less well understood in those conditions, we'll start with a small number of genes. Table 1 lists genes with relevant phenotypes and references for the interested reader [54-62].

CONCLUSION

As we have noticed that apparently easy phenomenon of ureteric budding may be an extremely difficult where positive and feedback circuit is used in this manner, which is rigorously controlled. As a result, it's not surprising that a significant number of genes are associated with the formation of urinary duplexes, and future research will almost certainly find more elements involved in these deformities. Yet, establishing mutations as disease-causing variations is becoming increasingly difficult due to poor trait entry and the multigenic foundation of this malformation. The information counsels that double ureter organ phenotypes could even be extremely dependent genetic scenario, pointing to the existence of genes that are changing. In addition to that, intragenic /regulatory mutations or epigenetic methods that have an effect on phenomenon levels instead of super molecule operate are probably to come up with the disease. In the end, we must keep in mind that, in spite of an oversized degree of conservation, people show important variations not only on the process but also on the molecular level. Future analysis should additionally address the inequality within the recurrence of double ureteric kidneys appearing in males and females. Within the longer term, the mixture of an oversized proportion of whole order series information yet as an improved comprehension of however gene regulation is attained are going to be needed to endorse the connection of genomic variations and forecast the constitution aftermath in duplex kidneys.

Tables 1: Genes involved in duplex kidney formation.

Group	Genotype	Mechanism
GNDF Domain		
	Robo2$^{-/-}$	Abnormal Gdnf expression domain MM fails to separate from WD
	Slit2$^{-/-}$	Abnormal Gdnf expression domain
	Foxc1$^{-/-}$	MM fails to reduce in size
	Sox11$^{-/-}$	MM fails to reduce in size
Increased sensivity of WD		
	Bmp4$^{+/-}$	lack of inhibition of WNT11, a target of GDNF
	lft25$^{-/-}$, lft27$^{-/-}$	increased sensitivity of WD through Germlin-BMP4 Cascade
	Gli3$^{\Delta 699/\Delta 699}$	increased sensitivity of WD through Germlin-BMP4 Cascade
	Agtr2$^{-/Y}$	Disrupted renin-angiotensin signalling leads to aberrant UB morphogenesis
	p53$^{-/-}$, p53$^{UB-/-}$	Increased response of WD to GDNF signal. Two ureters fuse in the later development and resemble a bifurcation
	Fat4$^{-/-}$ Fjx1$^{-/-}$	Premature branching with incomplete duplication due to overactive GDNF-RET signalling
	Hoxb7-Cre β-catenin$^{-/C}$	Ectopic activation of UB branching pathway in WD
	Spry1$^{-/-}$	increased sensitivity of WD to GDNF-Ret signalling
	Gata3ND$^{-/-}$	the entire length on WD is covered by ectopic UB's, most of which subsequently regress
Cell polarity detect		
	T-Cre Wnt5af$^{1/\Delta}$	Double UB, abnormal morphology of posterior WD, defects in IM morphogenesis
	Ror2$^{-/-}$	Similar to *Wnt5a* phenotype
	Cell adhesion defect	
	L1$^{-/Y}$	Either incomplete or complete duplication. Double UB in WD or accessory budding from the main ureter
Unknown		
	Pax2$^{+/-}$	Premature branching with incomplete duplication linked with inactivation of GDNF expression
	Pax2-Cre Lim1$^{\Delta/\Delta}$	WD fails to extend caudally; UB is absent or Y-shaped
	Cc2d2a, Mks1, Cep290, Dync2h1, Tbc1d32, Tmem67	Duplex kidney as a part of a ciliopathy phenotype
	Sox17$^{Y259N/+}$	Duplicated pyeloureteral collecting system
	Nfia$^{-/-}$	Partial ureteral duplication
	Adamts18$^{-/-}$	Complete ureteral duplication, increased nephron endowment

REFERENCES

1. Gonzalez F, Canning DA, Hyun G, Casale P. Lower pole pelvi-ureteric junction obstruction in duplicated collecting systems. BJU Int. 2006;97(1):161-165.
2. Nation EF. Duplication of the kidney and ureter: A statistical study of 230 new cases. J Urol. 1944;51(5):456-65.
3. Schlussel RN. Ectopic ureter, ureterocele, and other anomalies of the ureter. Campbell's urology. 2002.
4. Horst M, Smith GH. Pelvi-ureteric junction obstruction in duplex kidneys. BJU Int. 2008;101(12):1580-1584.
5. Ossandon F, Anbroulakakis P, Ransley PG. Surgical problems in pelvioureteral junction obstruction of the lower moiety in incomplete duplex systems. J Urol. 1981;125(6):871-872.
6. Georgas KM, Armstrong J, Keast JR, Larkins CE, McHugh KM, Southard-Smith EM, et al. An illustrated anatomical ontology of the developing mouse lower urogenital tract. Dev. 2015;142(10):1893-1908.
7. Grote D, Souabni A, Busslinger M, Bouchard M. Pax2/8-regulated Gata3 expression is necessary for morphogenesis and guidance of the nephric duct in the developing kidney.
8. Pedersen A, Skjong C, Shawlot W. Lim1 is required for nephric duct extension and ureteric bud morphogenesis. Dev Biol. 2005;288(2):571-581.
9. Attia L, Schneider J, Yelin R, Schultheiss TM. Collective cell migration of the nephric duct requires FGF signaling. Dev Dyn. 2015;244(2):157-167.
10. Chia I, Grote D, Marcotte M, Batourina E, Mendelsohn C, Bouchard M. Nephric duct insertion is a crucial step in urinary tract maturation that is regulated by a Gata3-Raldh2-Ret molecular network in mice. Dev. 2011;138(10):2089-2097.
11. Hoshi M, Reginensi A, Joens MS, Fitzpatrick JA, McNeill H, Jain S. Reciprocal spatiotemporally controlled apoptosis regulates Wolffian duct cloaca fusion. J Am So Nephrol. 2018;29(3):775-783.
12. Sainio K, Hellstedt P, Kreidberg JA, Saxén L, Sariola H. Differential regulation of two sets of mesonephric tubules by WT-1. Dev. 1997;124(7):1293-1299.
13. Mugford JW, Sipilä P, Kobayashi A, Behringer RR, McMahon AP. Hoxd11 specifies a program of metanephric kidney development within the intermediate mesoderm of the mouse embryo. Dev Biol. 2008;319(2):396-405.

14. Taguchi A, Kaku Y, Ohmori T, Sharmin S, Ogawa M, Sasaki H, et al. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. Cell Stem Cell. 2014;14(1):53-67.

15. Short KM, Combes AN, Lefevre J, Ju AL, Georgas KM, Lamberton T, et al. Global quantification of tissue dynamics in the developing mouse kidney. Dev Cell. 2014;29(2):188-202.

16. Dumbrava MG, Lacanlale JL, Rowan CJ, Rosenblum ND. Transforming growth factor beta signaling functions during mammalian kidney development. Pediatr Nephrol. 2021;36(7):1663-1672.

17. Oxburgh L. Kidney nephron determination. Ann Rev Cell Dev Biol. 2018;34:427-450.

18. Huang YC, Chen F, Li X. Clarification of mammalian cloacal morphogenesis using high-resolution episcopic microscopy. Dev Biol. 2016;409(1):106-113.

19. Kruepunga N, Hikspoors JP, Mekonen HK, Mommen GM, Meemon K, Weerachatyanukul W, et al. The development of the cloaca in the human embryo. J Anat. 2018;233(6):724-739.

20. Liaw A, Cunha GR, Shen J, Cao M, Liu G, Sinclair A, et al. Development of the human bladder and ureterovesical junction. Differ. 2018;103:66-73.

21. Glassberg KI, Braren V, Duckett JW, Jacobs EC, King LR, Lebowitz RL, et al. Suggested terminology for duplex systems, ectopic ureters and ureteroceles. J Urol. 1984;132(6):1153-1154.

22. Zissin R, Apter S, Yaffe D, Kots E, Gayer G, Nissenkorn I, et al. Renal duplication with associated complications in adults: CT findings in 26 cases. Clin Radiol. 2001;56(1):58-63.

23. Weigert C. Ueber einige bildungsfehler der ureteren. Arch Pathol Anat Physiol Klin Med. 1877;70(4):490-501.

24. Britt DB, Borden TA, Woodhead DM. Inverted Y ureteral duplication with a blind-ending branch. J Urol. 1972;108(3):387-388.

25. Akbulut F, Savun M, Ucpinar B, Sahan M, Arslan B, Ozgor F, et al. Duplicated renal system with H shaped ureter: An extraordinary anomaly. Case Rep Urol. 2016;2016.

26. Privett JT, Jeans WD, Roylance J. The incidence and importance of renal duplication. Clin Radiol. 1976;27(4):521-530.

27. Batourina E, Choi C, Paragas N, Bello N, Hensle T, Costantini FD, et al. Distal ureter morphogenesis depends on epithelial cell remodeling mediated by vitamin A and Ret. Nat Genet. 2002;32(1):109-115.

28. Uetani N, Bertozzi K, Chagnon MJ, Hendriks W, Tremblay ML, Bouchard M. Maturation of ureter-bladder connection in mice is controlled by LAR family receptor protein tyrosine phosphatases. J Clin Investig. 2009;119(4):924-935.

29. Batourina E, Tsai S, Lambert S, Sprenkle P, Viana R, Dutta S, et al. Apoptosis induced by vitamin A signaling is crucial for connecting the ureters to the bladder. Nat Genet. 2005;37(10):1082-1089.

30. Davis TK, Hoshi M, Jain S. To bud or not to bud: The RET perspective in CAKUT. Pediatr Nephrol. 2014;29(4):597-608.

31. Willecke R, Heuberger J, Grossmann K, Michos O, Schmidt-Ott K, Walentin K, et al. The tyrosine phosphatase Shp2 acts downstream of GDNF/Ret in branching morphogenesis of the developing mouse kidney. Dev Biol. 2011;360(2):310-317.

32. Perrinjaquet M, Vilar M, Ibáñez CF. Protein-tyrosine phosphatase SHP2 contributes to GDNF neurotrophic activity through direct binding to phospho-Tyr687 in the RET receptor tyrosine kinase. J Biol Chem. 2010;285(41):31867-31875.

33. Takahashi M. The GDNF/RET signaling pathway and human diseases. Cytokine & Growth Factor Rev. 2001;12(4):361-373.

34. Lu BC, Cebrian C, Chi X, Kuure S, Kuo R, Bates CM, et al. Etv4 and Etv5 are required downstream of GDNF and Ret for kidney branching morphogenesis. Nat Genet. 2009;41(12):1295-1302.

35. Xu PX, Adams J, Peters H, Brown MC, Heaney S, Maas R. Eya1-deficient mice lack ears and kidneys and show abnormal apoptosis of organ primordia. Nat Genet. 1999 Sep;23(1):113-117.

36. Hwang DY, Dworschak GC, Kohl S, Saisawat P, Vivante A, Hilger AC, et al. Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. Kidney Int. 2014;85(6):1429-1433.

37. 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.

38. Bridgewater D, Cox B, Cain J, Lau A, Athaide V, Gill PS, et al. Canonical WNT/β-catenin signaling is required for ureteric branching. Dev Biol. 2008;317(1):83-94.

39. Miyamoto N, Yoshida M, Kuratani S, Matsuo I, Aizawa S. Defects of urogenital development in mice lacking Emx2. Dev. 1997;124(9):1653-1664.

40. Wilkinson LJ, Neal CS, Singh RR, Sparrow DB, Kurniawan ND, Ju A, et al. Renal developmental defects resulting from in utero hypoxia are associated with suppression of ureteric β-catenin signaling. Kidney Int. 2015;87(5):975-983.

41. Gimelli S, Caridi G, Beri S, McCracken K, Bocciardi R, Zordan P, et al. Mutations in SOX17 are associated with congenital anomalies of the kidney and the urinary tract. Hum Mutat. 2010;31(12):1352-1359.

42. Kobayashi A, Kwan KM, Carroll TJ, McMahon AP, Mendelsohn CL, Behringer RR. Distinct and sequential tissue-specific activities of the LIM-class homeobox gene Lim1 for tubular morphogenesis during kidney development.

43. Miyazaki Y, Oshima K, Fogo A, Hogan BL, Ichikawa I. Bone morphogenetic protein 4 regulates the budding site and elongation of the mouse ureter. J Clin Investig. 2000;105(7):863-873.

44. Weaver M, Dunn NR, Hogan BL. Bmp4 and Fgf10 play opposing roles during lung bud morphogenesis. Dev. 2000;127(12):2695-2704.

45. Michos O, Gonçalves A, Lopez-Rios J, Tiecke E, Naillat F, Beier K, et al. Reduction of BMP4 activity by gremlin 1 enables ureteric bud outgrowth and GDNF/WNT11 feedback signalling during kidney branching morphogenesis. Dev. 2007;134(13):2397-2405.

46. van Eerde AM, Duran K, van Riel E, de Kovel CG, Koeleman BP, Knoers NV, et al. Genes in the ureteric budding pathway: Association study on vesico-ureteral reflux patients. PLOS One. 2012;7(4):e31327.

47. Desai PB, San Agustin JT, Stuck MW, Jonassen JA, Bates CM, Pazour GJ. Ift25 is not a cystic kidney disease gene but is required for early steps of kidney development. Mech Dev. 2018;151:10-17.

48. Blake J, Hu D, Cain JE, Rosenblum ND. Urogenital development in Pallister–Hall syndrome is disrupted in a cell-lineage-specific manner by constitutive expression of GLI3 repressor. Hum Mol Genet. 2016;25(3):437-447.

49. San Agustin JT, Klena N, Granath K, Panigrahy A, Stewart E, Devine W, et al. Genetic link between renal birth defects and congenital heart disease. Nat Commun. 2016;7(1):1-1.

50. Elliott KH, Brugmann SA. Sending mixed signals: Cilia-dependent signaling during development and disease. Dev Biol. 2019;447(1):28-41.

51. Basson MA, Akbulut S, Watson-Johnson J, Simon R, Carroll TJ, Shakya R, et al. Sprouty1 is a critical regulator of GDNF/RET-mediated kidney induction. Dev Cell. 2005;8(2):229-239.

52. Yosypiv IV, Boh MK, Spera MA, El-Dahr SS. Downregulation of Spry-1, an inhibitor of GDNF/Ret, causes angiotensin II-induced ureteric bud branching. Kidney Int. 2008;74(10):1287-1293.

53. Nishimura H, Yerkes E, Hohenfellner K, Miyazaki Y, Ma J, Hunley TE, et al. Role of the angiotensin type 2 receptor gene in congenital anomalies of the kidney and urinary tract, CAKUT, of mice and men. Mol Cell. 1999;3(1):1-10.

54. Lindström NO, Guo J, Kim AD, Tran T, Guo Q, Brandine GD, et al. Conserved and divergent features of mesenchymal progenitor cell types within the cortical nephrogenic niche of the human and mouse kidney. J Am Soc Nephrol. 2018;29(3):806-824.

55. Lindström NO, McMahon JA, Guo J, Tran T, Guo Q, Rutledge E, et al. Conserved and divergent features of human and mouse kidney organogenesis. J Am Soc Nephrol. 2018;29(3):785-805.

56. Lindström NO, Tran T, Guo J, Rutledge E, Parvez RK, Thornton ME, et al. Conserved and divergent molecular and anatomic features of human and mouse nephron patterning. J Am Soc Nephrol. 2018;29(3):825-840.

57. Aradhey P, Bakre A, Kumar S, Acharya S. Clinical profile of Uremic polyneuropathy in Chronic Kidney Disease patients. Med Sci. 2020;24(102):945-951.

58. Jain S, Phatak SV, Varma A, Dhande RP. Autosomal Dominant Polycystic Kidney Disease with Liver and Pancreatic Involvement. J Evol Med Dent Sci. 2020;9(20):1625-1627.

59. Jamthe A, Varma A, Mohale S, Acharya S, Andhale A, Annadatha A. Clinical Application of Fasting and Post-Prandial Lipid Profile in Patients of Chronic Kidney Disease. J Evol Med Dent Sci. 2020;9(36):2636-2641.

60. Prasad N, Bhatt M, Agarwal SK, Kohli HS, Gopalakrishnan N, Fernando E, et al. The adverse effect of COVID pandemic on the care of patients with kidney diseases in India. Kidney Int Rep. 2020;5(9):1545-50.

61. Singh K, Acharya N, Acharya S, Agrawal M. Latent Chronic Kidney Disease (CKD) Manifesting as Eclampsia in Elderly Primigravida. J Evol Med Dent Sci. 2020;9(47):3596-3598.

62. Somani A, Hathi D, Acharya S, Gupta A. Traumatic Rhabdomyolysis presenting as acute kidney Injury and acute Respiratory Distress Syndrome in young male athlete. Med Sci. 2020;24(102):771-775.