Genetic Basis of Congenital Anomalies of Kidney and Urinary Tract

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Abstract

Congenital anomalies of kidney and urinary tract (CAKUT) is a group of abnormalities affecting the kidneys or other structures of the urinary tract that include ureters, urinary bladder and urethra. CAKUT include renal agenesis or hypodysplasia, multicystic dysplastic kidney, ureteropelvic junction obstruction, duplication of the pelvis, ureter, and/or kidney, congenital megaureter, ureterovesical junction obstruction, vesicoureteral reflux and posterior urethral valves. Those results from abnormal development of the urinary system and is present from birth (congenital), although the abnormality may not become apparent until later in life. The clinical spectrum of CAKUT has significant impact on long-term patient survival. We observed that the causes of CAKUT are complex, usually combination of genetic and environmental factors contribute to the developmental abnormalities of kidney and urinary tract in foetus. The genetic factors involved in most cases of CAKUT are unknown; however, syndromic CAKUT is caused by changes in the genes associated with the particular syndrome. Variations in the same genes can also underlie some cases of isolated CAKUT. This review paper aims to discuss genetic basis of CAKUT, i.e., identifying different genes involved in syndromic and non-syndromic CAKUT. Modern genetic testing facilities can provide a precise diagnosis that can help individualize clinical care by screening for specific complications, facilitate medical decision making, and provide better genetic counseling.

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Introduction

Congenital anomalies of kidney and urinary tract (CAKUT) is a group of abnormalities affecting the kidneys or other structures of the urinary tract that include ureters, urinary bladder and urethra.[1] CAKUT results from abnormal development of the urinary system and is present from birth (congenital), although the abnormality may not become apparent until later in life.[1-3] In clinical settings, CAKUT include renal agenesis or renal hypodysplasia (RHD), multicystic dysplastic kidney (MCDK), ureteropelvic junction obstruction (UPJO), duplication of the pelvis, ureter, and/or kidney (DCS), congenital megaureter, ureterovesical junction obstruction (UVJO), vesicoureteral reflux (VUR), and posterior urethral valves (PUVs).[1-6] Studies have shown that different structural defects have distinct impacts on long-term renal survival and overall mortality, with RHD conferring the greatest risk of

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adverse events.[1-8]

The development of the mammalian kidney during embryonic life is a multi-stage process that derives from reciprocally inductive events between two intermediate mesenchymal progenitors: the ureteric bud (UB) and the metanephric mesenchyme (MM). It begins at 35-37 days of gestation in humans with the induction of the ureteric bud from the nephric duct, followed by mesenchymal to epithelial transition (MET) and branching morphogenesis, and terminates with nephron patterning and elongation (which include proximal and distal tubule morphogenesis and glomerulogenesis).[9-11] These embryologic events require a tight regulation at the DNA level (mediated by transcriptional factors) and the post-transcriptional level, and as mentioned above, perturbation in each of those steps, due to exposure to environmental risk factors or to the dysfunction of genes that direct this process, can lead to CAKUT.[4,6] Malformations in CAKUT can affect single or multiple structures in a symmetric or asymmetric fashion, with significant variability between individuals carrying the same mutation.[12]

This review paper is a modest effort to highlight some of the recent findings on genetic basis of CAKUT and its diagnostic modalities to increase the knowledge pool, which will help our physicians develop their capabilities to diagnose, treat, and prevent of congenital renal system anomalies and their consequences.

Epidemiology

CAKUT is identified in more than 1% of overall live births, accounting for up to 23% of overall birth defects in humans.[13,14] It is estimated globally that 40% to 50% of paediatric and 2% to 7% of adult end-stage renal disease (ESRD) is attributable to CAKUT.[15-20]

However, a number of extrinsic factors including maternal diabetes, medications, and folate and iron deficiency also increase the risk of CAKUT, highlighting environmental factors that modify expression of disease.[21-24] When ESRD is present at birth, mortality rates reach a striking 93% within the first year of life, and children who survive infancy have a 30-fold higher mortality compared with same-age children without ESRD.[25-28] These population data underline the enormous impact of CAKUT on child health. Substantial improvement in early clinical care, such as prenatal detection of CAKUT by fetal ultrasonography and development of surgical and pharmacological approaches, has dramatically improved survival for infants and children with renal failure.[6,18,29] This, in turn, will result in a decreased number of adult patients with further complications of CAKUT.[29]

Aetiology

The causes of CAKUT are complex. It is more likely that a combination of genetic and environmental factors contributes to the developmental abnormalities of kidney and urinary tract in foetus.[3,4,21-24] Implementation of next generation sequencing in research and diagnostic settings has led to the identification of the molecular basis of many developmental diseases.[2] However, the genetic factors involved in most cases of CAKUT are unknown. Syndromic CAKUT is caused by changes in the genes associated with the particular syndrome, while variations in those same genes can also underlie some cases of isolated CAKUT.[3,4,8,30-33] For example, the genes most commonly associated with isolated CAKUT are PAX2, which is also associated with renal coloboma syndrome, and HNF1B, which is involved in 17q12 deletion syndrome and RCAD syndrome.[31-33] These two

genes play critical roles in the formation of the kidneys, urinary tract, and other tissues and organs during embryonic development. Certain mutations in these genes are thought to disrupt development of the kidneys or other parts of the urinary tract before birth, leading to CAKUT.[4,31-33] Besides, mutations in many other genes involved in development of the urinary system have also been associated with isolated or syndromic CAKUT.[34-43] Table-I outlines some of the important genes involved in syndromic and non-syndromic CAKUT.

Research shows that the same genetic mutation can lead to different kidney or urinary tract abnormalities, even among members of the same family.[4,8,31] In addition, as we have discussed earlier, environmental factors may influence development of CAKUT. The risk of CAKUT is higher in babies whose mothers had diabetes; took certain medications that are harmful to the kidneys, such as some anti-seizure drugs; or lacked certain vitamins and minerals, such as folate and iron, during pregnancy.[21-24]

Pattern of Inheritance

Inheritance of CAKUT is a bit complex in nature and not completely understood to date. However, evidence showed that about 10 to 20 percent of cases occur in families.[6,18,29] When inherited, CAKUT usually follows an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause an abnormality. However, some people who have the altered gene never develop CAKUT, which is termed as reduced penetrance.[18,29,31] Less commonly, CAKUT follows an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they hardly show signs or symptoms throughout the life. In many cases, the inheritance pattern is unknown, or the condition is not inherited.[18,29,31,44] Surprisingly, in some of these cases, a new (de novo) mutation in the gene that occurs during the formation of reproductive cells (eggs or sperm) in an affected individual's parent or in early embryonic development may underlie the urinary system abnormality. That happens in people with no clue or history of such disorder in their family.[18,31,44,45]

Table-I: Different genes involved in syndromic and non-syndromic CAKUT[4,5,8,31-43]

Gene(s)	Disease
ACE, AGT, AGTR1, REN	Renal tubular dysgenesis
BMP4, DSTYK, SOX17	CAKUT
EYA1	Branchio-oto-renal syndrome and renal hypoplasia
FRAS1, FREM1, GRIP1	Fraser syndrome
FREM1	Bifid Nose Renal Agenesis and Anorectal malformations (BNAR) syndrome
HNF1β	Multicystic dysplastic kidney, renal hypoplasia, renal cysts and diabetes syndrome
NOTCH2	Alagille syndrome, renal anomalies
PAX2	Renal coloboma syndrome and CAKUT
RET	Renal agenesis and Hirschsprung disease
SALL1	Townes-Brocks Syndrome
SALL4	Duane-radial ray syndrome
SIX1, SIX5	Branchio-oto-renal Syndrome
SIX2	Renal hypodysplasia
UPK3A	Renal dysplasia
WNT4	Mullerian aplasia and hyperandrogenism
UMOD	Familial juvenile hyperuricemic nephropathy (FJHN), glomerulocystic kidney disease (GCKD), Autosomal dominant medullary cystic kidney disease 2 (MCKD2)

Implications in Clinical Care

An understanding of the genetic aspects of human CAKUT will help to unravel the pathogenesis of these disorders and may facilitate the design of genetic screening tests for early diagnosis and appropriate genetic counseling.[1,6,18,29,31] Now-a-days clinicians have the opportunity to incorporate genetics into their diagnostic workup with advanced technologies like clinical grade chromosomal microarray and next-generation sequencing.[6,18] Candidate gene and whole exome sequencing, and genome-wide linkage and copy number variant (CNV) analyses may help to discover genetic causes of CAKUT.[12,31] Genetic testing can provide a precise diagnosis that can help individualize clinical care by screening for specific complications (e.g., screen for diabetes or ocular coloboma in patients with HNF1B and PAX2 mutations, respectively)[24,32,33] and facilitate medical decision making (e.g., avoiding immunosuppressive therapy in CAKUT clinically misdiagnosed as a glomerular nephropathy because of low-grade proteinuria). The availability of genetic diagnosis also facilitates lowering diagnostic odysseys for families and paves the way to proper genetic counseling.

Conclusion

Integrated understanding of genetic factors and morphogenesis disruptions linked to CAKUT will enable improved diagnosis, treatment, and prevention of congenital renal system anomalies and their consequences. Moreover, importance of sound knowledge of the genetics of the congenital anomalies of kidney and urinary tract (CAKUT) is that CAKUT is only the first manifestation of a complex systemic disease and can manifest in different members of the same family. Modern genetic testing facilities can provide a precise diagnosis that can help individualize clinical care by screening for specific complications, facilitate medical decision making, and provide better genetic counselling.

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