Liječ Vjesn 2022;144;suplement 1:165–166
https://doi.org/10.26800/LV-144-supl1-26

Pregled | Review

Congenital anomalies of the kidney and urinary tract (CAKUT)

Prirođene anomalije bubrega i urinarnog trakta (CAKUT)

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Key words
CONGENITAL, ANOMALIES;
KIDNEY;
URINARY TRACT

SUMMARY. Congenital anomalies of the kidney and urinary tract (CAKUT) are wide spectrum of prenatal malformations (isolated or as a part of syndromes), accounting for up to one quarter of overall birth defects and causes end-stage renal disease in up to a half of these cases. The most sever CAKUT phenotypes arise from a disturbed differentiation or interaction of the ureteric bud and the metanephric mesenchyme. CAKUT can be triggered through interplay of various genetic and epigenetic factors, as well as by numerous extrinsic factors including maternal diabetes, medications, and folate and iron deficiency, highlighting environmental factors that modify expression of disease. Genetic impairments (about 40 monogenic isolated and about 150 as a part of a syndrome) underlay about 15% of cases with variable expressivity and incomplete penetrance. Copy number variations (CNVs) and submicroscopic chromosomal imbalances are diagnostic challenge. Early identification of mutations in genes which can lead to CAKUT can facilitate targeted therapy. Gene panels based on next generation sequencing technology (NGS) might elucidate and significantly improve the process of testing and may lead to proper and thereby more effective diagnosis of CAKUT.

Ključne riječi
PRIROĐENE, ANOMALIJE;
BUBREG;
URINARNI TRAKT

SAŽETAK. Kongenitalne anomalije bubrega i urinarnog trakta (CAKUT) predstavljaju širok spektar prenatalnih malformacija (izoliranih ili u sklopu sindroma), koje čine do jedne četvrtine ukupnih urođenih mana i uzrokuju završnu bubrežnu bolest u do polovice ovih slučajeva. Najteži CAKUT fenotipovi proizlaze iz poremećene diferencijacije ili interakcije mokraćovodnog pupoljka i metanefričkog mezenhima. CAKUT može nastati međudjelovanjem različitih genetskih i epigenetskih čimbenika, kao i zbog brojnih vanjskih čimbenika kao što su dijabetes majke, lijekovi, nedostatak folata i željeza, uz naglasak na čimbenike okoliša koji modificiraju ekspresiju bolesti. Genetski poremećaji (oko 40 izoliranih gena i oko 150 koji su dio sindroma) su u pozadini oko 15% slučajeva s promjenjivim izražajem i nepotpunom penetrantnosti. Varijacije broja kopija i submikroskopske kromosomske neravnoteže predstavljaju dijagnostički izazov. Rano prepoznavanje mutacija u genima koje mogu dovesti do CAKUT-a olakšali bi ciljanu terapiju. Paneli gena temeljeni na tehnologiji sekvenciranja sljedeće generacije mogli bi razjasniti i značajno poboljšati proces testiranja i dovesti do ispravne i učinkovitije dijagnoze CAKUT-a.

Congenital anomalies of the kidney and urinary tract (CAKUT) comprise a clinically wide spectrum of malformations and are among most identified prenatal defect, accounting for up to 23% of overall birth defects[1,2]. CAKUT can present as an isolated renal condition or as a part of a syndrome[3]. The incidence of CAKUT is approximately 1 to 4 per 1000 pregnancies[3]. About 40% to 50% of pediatric and 7% of adult end-stage renal disease are thought to be caused by CAKUT[3]. Among the most prevalent CAKUT subtypes are kidney agenesis, hypodysplastic kidneys, hydronephrosis, megaureter, duplicated ureter, ureteropelvic junction obstruction (UPJO), and vesicoureteral reflux (VUR), ureterovesical junction obstruction (UVJO), or posterior urethral valves (PUV)[4]. Although some of them are clinically insignificant, about half of chronic kidney disease (CKD) patients below 18 years of age are result from CAKUT[4].

The most sever CAKUT phenotypes arise from a disturbed differentiation or interaction of the ureteric bud and the metanephric mesenchyme, while the less sever defects arise later during the development[5–7]. CAKUT can be triggered through interplay of various genetic and epigenetic factors, as well as by numerous extrinsic factors including maternal diabetes, medications, and folate and iron deficiency, highlighting environmental factors that modify expression of disease[1]. Because of wide genetic heterogeneity the etiology of CAKUT often remain unknow, but it is thought to be multifactorial in many cases[5].

Genetic conditions underlying CAKUT contribute to disease etiology in ~ 16% of children with CAKUT[4]. While most cases of CAKUT seems to be sporadic, about 15% demonstrate familial aggregation, typically

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inherited in autosomal dominant order, with variable expressivity and incomplete penetrance. A smaller number of familial cases are inherited in autosomal recessive order, usually as syndromic CAKUT[4]. Until now, about 40 monogenic causes for CAKUT as an isolated renal condition and about 150 monogenic causes of CAKUT as a part of a syndrome have been identified[3]. Some of single-gene causes of isolated CAKUT are mutations in *HNF1B, PAX2, EYA1, SALL1, GATA3* and *PBX1* genes[4]. Mutations in *KMT2D, EP300, NOTCH2, CHD7, ANOS1* and many other gene have been identified as single-gene causes of syndromic CAKUT[4]. CAKUT as a phenotypic component may be included in more than 150 different rare multiorgan syndromes, e.g. Potter syndrome, Fraser syndrome, Allagille syndrome, Pallister-Hall syndrome, Kallmann syndrome, Prune-belly syndrome[4,8]. The etiology of CAKUT often involves copy number variations (CNVs), submicroscopic chromosomal imbalances which are usually challenged to identify[4]. For example, deletion at the 22q11.2 locus was found as the culprit for CAKUT in DiGeorge syndrome as well as in sporadic cases of CAKUT. In this region, CRKL appears to be the critical driver for the kidney phenotype[4,9].

It is suspected that approximately 20% of patients may have a genetic disorder that is not detected by standard clinical examination, implicating even higher number of different mutational mechanisms and pathogenic pathways that may cause CAKUT[1]. Everyone with familial cases, syndromic cases, persons with kidney failure or significant extra-kidney malformations should be encouraged to perform genetic counselling and genetic testing[4]. Early identification of mutations in genes which can lead to CAKUT can facilitate targeted therapy[3]. Gene panels based on next generation sequencing technology (NGS) allow the study of multiple genes together, thus significantly improve the process of testing[3]. The mainstay for the discovery of new genes in various kidney disorders is whole exome sequencing (WES). However, some molecular changes could be happened in the introns, or due to copy number changes and these could reliably be studied only by whole genome sequencing, which can analyse all the introns and the exons[3].

Understanding of the pathophysiology and the natural history of CAKUT is challenging as it comprises a broad clinical conditions without a clear understanding of developmental etiology[10]. As we are entering in postgenomic era of personalized medicine, genetic testing may lead to proper and thereby more effective diagnosis of CAKUT, providing a greater chance of delaying or even avoiding renal impairment[11,12]. Furthermore, clinical care is improved thanks to the decreased costs of whole genome sequencing and numerous valuable results from the studies focused on the genotype-phenotype correlations and animal models of the gene mutations[13]. Even a small volume of collected urine is respectable source for reprogrammable somatic cells that can be utilized to generate induced pluripotent stem cells (iPSC) and consequently to generate kidney organoids, which are a promising tool to investigate genetic mechanisms underlying CAKUT conditions[14]. iPSC and kidney organoids are valuable models in the discovering and screening new drug compounds, thereby contributing to development of personalized drug treatment[15]. In the light of all these findings we can conclude that multidisciplinary team approach is required to diagnose and treat these complex disorders.

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