CAKUT are mono-genetic diseases with a wide heterogeneous clinical presentation. Nowadays we are able to genetically explain only 10-16% of CAKUT cases by mutations or copy number variation (CNV). These two paper propose new approaches to improve genetic diagnosis in CAKUT.

Genetic, environmental, and epigenetic factors involved in CAKUT
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This paper is an interested review and update on CAKUT. Genetics of CAKUT is complex and consensus needs to be found to facilitate CAKUT diagnosis. This article offers a comprehensive understanding of known factors involved in CAKUT and gives keys to progress in the possibility to develop an ideal genetic strategy for CAKUT diagnosis in clinical practice, facilitate early diagnosis and genetic counseling.

Prevalence of CAKUT is estimated 6 per 1000 births. Successful prenatal detection of CAKUT has improved with availability and ultrasound performance but still remain under diagnosed. Our understanding of pathogenesis in CAKUT and genes involved in kidney development came from mouse models. European Renal registry showed that CAKUT is the leading cause of ESRD in children and account for 41.3% of children with RRT. In adult ESRD secondary to CAKUT account for 2.2% but the rate is most probably underestimated.

Summary of proposed genetic approaches to discover new genes
The Candidate genes are less successful for syndromic CAKUT than non-syndromic CAKUT. The number of genes and variants is overestimated and did not always imply pathogenicity. *Targeted next-generation sequencing* may be useful in identifying sporadic cases of CAKUT. This analysis has showed that <10% pts with isolated CAKUT carry variants in known genes (HNF1B, PAX, EYA1, SIX5, RET). Thus highlight that the majority of CAKUT causes are still not diagnosed. In the mean while, novel variants requiring functional characterization increase.
Whole exome sequencing in a candidate-free approach has led to identification of new CAKUT genes. Databases are available and report patients with similar phenotypes with exome sequencing done in different center but with the same variant candidate and share information.
Copy number variation is associated with elevated risk of CAKUT, *and should be part of the diagnosis procedure.* However CNV's and single gene mutation do not explain the majority of sporadic cases of CAKUT and complex interaction of environmental and epigenetic factors probably participate in the development of CAKUT.
Environment factors, as for example, the increase risk to present kidney agenesis in fetuses from mother with diabetes mellitus. Animal models have support the effect of maternal diabetes mellitus in CAKUT risk as hyperglycemia is inversely correlated with reduce nephron endowment. *Epigenetic* modifications have been postulated as mechanism that facilitates the interaction between environment factors during development with the genome, and its impact on disease susceptibility. Epigenetic include DNA methylation. These modifications modulate the structure of the chromatin and change its accessibility to transcription factors thus modifying the expression of genes. Gene expression levels during development can be affected by CNV's or single nucleotide changes locates *within enhancers miRNAs.*

To enhance CAKUT diagnosis, authors proposed an approach which include candidate gene and whole exome sequencing, genome–wide linkage and copy number variation. Epigenetic and gestational environment risk factors increase susceptibility to CAKUT and these point present novel opportunities to understand diseases mechanisms as they might explain interaction between genetics and environment and how variable penetrance might occur. The primary purpose is to develop an ideal diagnostic approach to CAKUT genetic to improve clinical practice and effort needs to be done to identify epigenetic biomarkers to favor therapeutic intervention.

Targeted sequencing of 96 renal developmental microRNAs in 1213 individuals from 980 families with congenital anomalies of the kidney and urinary tract
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In CAKUT, monogenic approach fails to explain 70-80% of cases and there are still a larger number of cases that cannot be genetically solved by mutations in coding genes. Knock out mouse models, lacking components of

the micro RNAs (miRNA) gene regulation during kidney may cause CAKUT. The hypothesis of the study was that as miRNAs are specifically expressed in nephrogenic tissue during kidney development, they may be responsible of CAKUT cases.
Candidate miRNA were selected on publishing miRNA expression profile in neprhogenic tissue. Authors analyzed by NGS-based targeted sequencing 96 stem loop regions of 73 renal development miRNA genes ("kidney miRNA"), in a large number of CAKUT pts (1213 individuals from 980 families). A total of 492 individuals were considered as having familial CAKUT according to clinical questionnaires. After quality controls, 31 individuals with 17 different single nucleotide variants affecting 16 different miRNA genes were identified. Only two out of 17 variants were found to be potentially pathogenic: MIR19B1 (renal agenesis) and MIR99A (VUR).
The authors conclude that
1. The "kidney miRNA "examined are well conserved by evolution
2. That point mutation most likely do not play an important role in human CAKUT

The limitation of the study, as reported in the paper, was the choice of a candidate approach that missed causative mutation of miRNA, since this approach does not detect CNV and large genetic rearrangement.
In futures studies, unbiased sequencing approach needs to confirm this statement (i.e. whole genome or exome + non coding RNAs).