miRNA-free rare pathogenic CNVs could drive toward variable CAKUT phenotypes

I. Zivotic[1], I. Kolic[1], K. Popic[1], J. Filipovic Trickovic[2],
A. Djordjevic[1], M. Zivkovic[1], A. Stankovic[1], I. Jovanovic[1]

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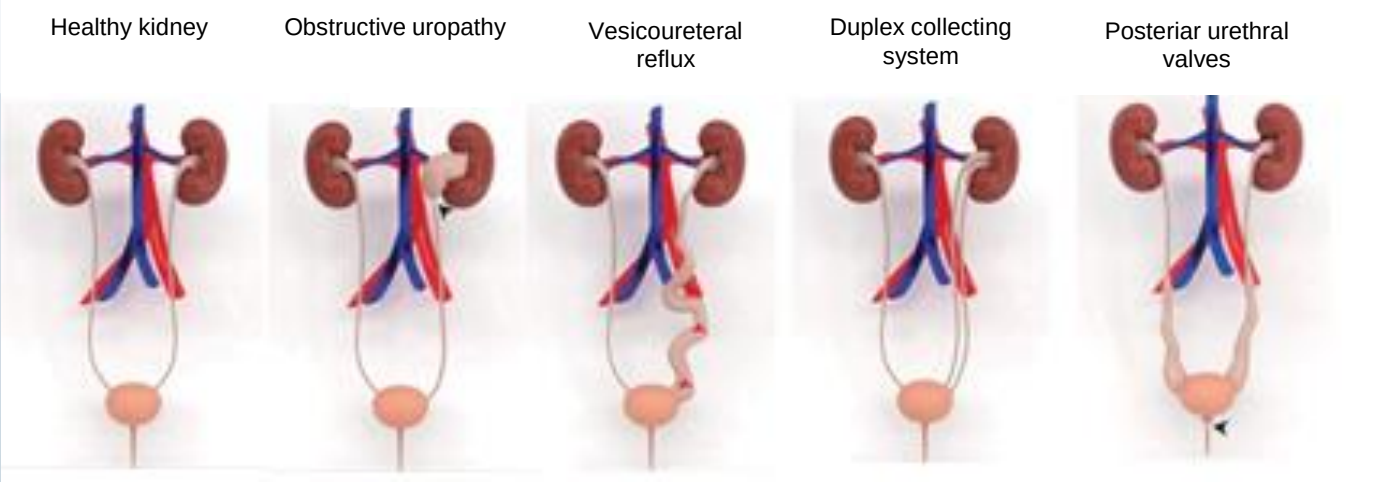
[1]Department of radiobiology and molecular genetics, "Vinča" Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade
[2]Department of physical chemistry, "Vinča" Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade

- **Introduction:** Genetic studies of congenital anomalies of the kidney and urinary tract (CAKUT) have demonstrated variable penetrability and expressivity of the associated genetic defects. Previously, it was shown that deletions of 17q12 and 22q11.2 regions were specific for kidney anomalies (KA) while 16p11.2 and 1q21.1 loci showed extensive pleiotropy in CAKUT phenotypes (obstructive uropathy, OU; vesicoureteral reflux, VUR; duplication collecting system, DCS; posterior urethral valves, PUV). Copy number variations (CNVs) affecting miRNA gene dosage have been described to have functional influence on gene expression.



Picture modified from Nicolaou et al. 2015.

Aim of the study: to conduct comprehensive in silico analysis using publicly available databases to analyze miRNA content of CAKUT-associated rare CNVs in quoted chromosomal loci with regard to CAKUT pleiotropy.

• Methods:

- Extensive literature review was conducted to collect data about pathogenic rare copy-number variants (rCNVs) associated with CAKUT.
- UCSC genome browser tool was employed for mapping miRNAs onto collected pathogenic rCNV regions. Data was accessed in January 2021, using genome assembly GRCh37 (hg19).
- Data was analyzed using R statistics software with in house developed scripts.

• Results:

1. Analysis of CNVs in CAKUT included four studies (Verbitsky et al. 2015, Verbitsky et al. 2018, Sanna-Cherchi et al. 2012, Maiying et al. 2019) counting more than 2500 patients. We selected group of 191 patients harboring rare pathogenic CNVs.
2. Total discovered number of different miRNA gene loci mapping on identified CNVs was 186.
3. Chromosomal region **22q11.2** was the most heterogeneous by the presence of different miRNA gene loci (n=21).
4. Most frequent CNVs in CAKUT patients were the chromosomal regions **17q12 (16.17%)** and **22q11.2 (8.82%)**.
5. Chromosomal regions **1q21.11** and **16p11.2**, previously marked as pleiotropic, did not contain any miRNA.

Conclusions:

- Absence of miRNAs may potentially pronounce the pleiotropy of the CAKUT genetic defects, thus leading to the variety of phenotypes.
- Contrary, abundancy of miRNAs in 22q11.2 might be associated with reproducible phenotype, such as kidney anomalies, producing the functional effect when deleted.

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