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Genomic microimbalances in children with combined congenital heart and kidney defects

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Introduction: Combined congenital defects of cardio-vascular system and renal-urinary tract belong to severe and relatively rare clinical conditions that represent isolated cases or can be a part of complex congenital syndromes. By now, several studies on the prevalence of such conditions have been performed and the high rate of co-occurrence of congenital heart defects and kidney abnormalities was confirmed implying a genetic link between the two types of malformations. Spectrum of causative genes and molecular mechanisms leading to cardio-renal defects still remain to be elucidated.

Purpose: In the present work we evaluated the impact of subtle genomic imbalances in 35 children (age 0-17 years) who presented with combined heart and kidney birth structural defects without additional severe organ manifestations.

Methods: High-resolution molecular-cytogenetic analysis was performed using oligonucleotide array-based comparative genomic hybridization (array-CGH) on 60K platform with median probe spacing 41 kb.

Results: In 2 out of 35 screened patients, a heterozygous deletion of ~2.47 Mb in size was identified in the 22q11.2 region known as DiGeorge/Velocardiofacial locus. These findings support the utility of screening for 22q11.2 deletion among the children with non-syndromic cardio-renal structural defects not often described for classical 22q11.2 deletion syndromes. A newborn with hypoplastic left heart syndrome, mitral atresia, ventricle sept defect and congenital megaloureter harbored a microduplication at 15q26.2 region encompassing MCTP2 gene. It had been recently shown that MCTP2 represent a dosage-sensitive gene essential for proper left ventricular outflow tract development in frog X. laevis. Here for the first time, we describe a MCTP2 duplication in association with combined cardio-renal malformations and suggest that this micro-rearrangement is responsible for at least a cardiac component of the patient’s phenotype. Additionally, we took notice of genes NNT, DHFR, ZNF649 and NPHP1 within the copy number gains at 5p12 (~730 kb), 5q14.1 (~680 kb), 19p13.33 (~350 kb) and 2q13 (~140 kb) regions. The genes are shown to widely express in heart and kidney and play different important roles in embryogenesis. To determine with certainty the clinical significance of these microimbalances, further comprehensive functional studies are required.

Conclusion: Our findings support the utility of array-CGH screening of patients with combined structural cardio-renal defects for more accurate individual diagnosis and genetic counseling as well as for new candidate genes identification.