To detect copy number variants (CNVs) in patients with congenital heart defects (CHD) and identify potential novel candidate genes involved in CHD pathogenesis. CHD are the most common congenital anomalies. Etiology of CHD can be genetic (chromosomal abnormalities, rare single gene disorders) or environmental, but it is mostly multifactorial. Copy number variants (CNVs) are important causes of genetic syndromes associated with CHD. Chromosomal microarray (CMA) is used as the first test to detect the CNVs in this category of patients.

We have evaluated 260 subjects with CHD in the period between Jan 2016 and Sep 2019 using CMA. In the majority of cases additional features such as facial dysmorphia, intellectual disability/developmental delays (ID/DD) or extracardiac anomalies (ECA) (190/260; 73.1%) were present; the remainder had isolated CHD. CMA analysis was performed using Agilent SurePrint G3 Unrestricted CGH ISCA v2 Human Genome, 8x60 K oligonucleotide microarray format according to the manufacturers’ instructions (Agilent Technologies, USA).

Copy number variants were detected in 71 (71/260, 27.3%) patients; 53 of them (53/71, 74.6%) were classified as pathogenic and 18 (18/71, 25.4%) as variants of unknown clinical significance (VUS). Pathogenic CNVs were predominately deletions (36), followed by duplications (9) and complex rearrangements (8). CNVs were discovered in 4 patients with isolated CHD (4/70, 5.7%) and 67 patients with additional features (67/190; 35.3%). The most frequent pathogenic CNV was 22q11.21 deletion (DiGeorge syndrome), followed by other well-known syndromes (Williams, 5p deletion etc.). Beside these, we detected CNV clusters in loci that have previously been associated with CHD in literature such as 15q11.2, 8p23.1, 1q43 etc. We also observed rare CNVs in loci that have not yet been recognized as important in CHD pathogenesis. Potential novel candidate genes in these loci warrant further research.

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KABUKI SYNDROME: REVIEW OF THE CLINICAL FEATURES AND DIAGNOSTIC FINDINGS IN FOUR CROATIAN PATIENTS
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Goal Kabuki syndrome (KS) is a rare malformation syndrome caused by mutations in KMT2D and KDM6A genes. Besides the cardinal manifestations, including distinctive facial appearance, mild-to-moderate intellectual disability, dermatoglyphic abnormalities such as persistence of fetal fingertip pads, skeletal anomalies and postnatal growth retardation, a wide spectrum of other anomalies is documented so far. We present clinical features and diagnostic findings in our four patients.

Methods During the 2016-2019 period, four of our patients were diagnosed with KS based on clinical observation and gene-targeted testing or comprehensive genomic testing (exome sequencing).

Results Three of our patients were males, one aged 17 and two aged 3 years, and one female aged 16 years at the time of diagnosis. Mutation of the KMT2D gene was identified in two patients, mutation KDM6A in one patient, while molecular analysis of one male patient is still in progress.

In addition to the five cardinal findings, one male patient had cleft palate, one had aorto coartation with bicuspid aortic valve and one had multiple severe respiratory infections. Although susceptibility to autoimmune disorders is a known feature in these patients, our female patient with KMT2D gene mutation was recognized as the first KS patient with systemic lupus erythematosus.

Conclusion KS is a rare disorder with highly variable clinical features making the diagnosis difficult. Consequently, a close collaboration between pediatric subspecialists, clinical geneticists and molecular biologists is essential in the terms of clinical recognition and genetic confirmation of this syndrome.

Kabuki Syndrome - Old and New Evidence of Secondary Mitochondrial Dysfunction
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The oculocerebrorenal syndrome of Lowe (LS) is a rare, progressive, multisystemic X-linked disorder caused by mutations in OCRL gene. Patients classically present with ocular abnormalities including bilateral congenital cataracts and glaucoma, intellectual delay, severe generalized hypotonia with absent tendon reflexes, and proximal renal tubular dysfunction. Congenital bilateral cataracts and hypotonia are present at birth in almost all patients, while other classical symptoms develop gradually with variable severity. Consequently, differential diagnosis in infant period in these patients can be broad including other rare metabolic and neurologic disorders.

Herein we present a 4.5 year old boy with Lowe syndrome caused by novel mutation of OCRL gene (c.643C>T/p. Gln215*) initially diagnosed as having mitochondrialopathy due to alteration of mitochondria on electron microscopic examination in different tissues and decreased values of mitochondrial energy metabolism measurements in muscle. No pathogenic mutations in mitochondrial DNA were found on whole exome sequencing.

This patient recall historical hypothesis of secondary mitochondrial dysfunction in Lowe syndrome, that may be caused/intensified some of disease symptoms.

Low Syndrome: Old and New Evidence of Secondary Mitochondrial Dysfunction
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FIVE-YEAR UPDATE FOR THE PHASE III VORETIGENE NEPARVOVEC STUDY IN BIALLELIC RPE65 MUTATION-ASSOCIATED INHERITED RETINAL DISEASE
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Goal To determine whether ambulatory navigation, light sensitivity, and visual field (VF) improvements 1 year after voretigene neparvovec (VN) administration in patients with biallelic RPE65 mutation-associated inherited retinal dystrophy (IRD) are maintained at 5 years and review safety outcomes over the entire period.

Methods This is an open label, randomized, controlled Phase III trial performed at 2 sites in the United States. Patients were randomized to either original intervention (OI: bilateral subretinal VN at baseline; n=20) or delayed intervention (DI: VN after 1 year; n=9). The primary endpoint was bilateral