**Diagnostic Exome Sequencing in Pediatric Patients with Congenital Heart Disease**

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**Introduction:** Since 2011, diagnostic exome sequencing (DES) has proven beneficial in providing molecular diagnoses for patients with a spectrum of previously undiagnosed genetic diseases. Congenital heart defects (CHD) are a common comorbidity in Mendelian disorders, with pathogenic mutations increasingly found. This study aimed to evaluate the clinical utility of DES and to characterize the pathogenic findings in an unselected cohort of pediatric patients with CHDs.

**Methods:** In an unselected sample of 1064 pediatric patients referred for DES, result were compared for patients with and without CHDs; results categories were determined according to predefined diagnostic variant assessment (Farwell et al., 2014).

**Results:** 134 patients (12.6%) had CHDs, 930 did not (87.4%). Positive/likely positive results were identified in 33/134 (24.6%) patients with CHDs compared to 274 without CHD (29.5%) (p=0.26). Novel genetic etiologies were identified in 4/134 (3.0%) compared to 53 without CHD (5.7 %) (p=0.22). Uncertain findings were reported in 18/134 (13.4%) patients with CHDs and without CHD (n=78; 8.4%) (p=0.07). Overall negative DES results were reported in 79/134 (59.0%) patients with CHDs vs. without CHD 525 (56.5%) (p=0.64).

Pathogenic alterations were identified in 38 unique genes. Eight patients with CHD had dual diagnoses compared to dual diagnoses in 8 individuals without CHD (p=0.0003).

**Conclusion:** The diagnostic yield in pediatric patients with CHD (24.6%) is comparable to diagnostic yield of exome sequencing overall. All patients referred for DES with CHD were syndromic, with multiple organ involvements. The findings of dual diagnoses in patients with CHD compared to those without are very statistically significant (p=0.0003), suggesting a significant role for DES in patients with syndromic CHD, as a targeted gene approach may miss additional genetic etiologies. Herein, clinicians involved in the care of CHD, particularly in the presence of additional congenital anomalies, may utilize DES as an effective diagnostic tool, and should be aware that patients with CHD and additional organ system involvements may have more complex genetic diagnoses.