Diagnostic and Research Utility of Whole Exome Sequencing for Cardiac Disease

Gloria T. Haskell1, Brian C. Jensen3, Cecile Skyzyria1, Daniel S. Marchuk1, Leigh Ann Samsa1, Wei Huang5, Chris Bizon4, Kirk C. Wilhelmsen1,2, Karen Weck1, James P. Evans1 and Jonathan S. Berg1
1. Department of Genetics, UNC-Chapel Hill 2. Renaissance Computing Institute, Chapel Hill, NC, 3. UNC McAllister Heart Institute

- The North Carolina Genomic Evaluation by Next-Generation Exome Sequencing clinical trial, NCGENES, has enrolled 30 patients suspected of having a genetic cardiac condition, and is evaluating the use of whole exome sequencing (WES) as a diagnostic tool.
- Step1: The Diagnostic Sweep: Identify pathogenic variants in genes known to be associated with the patient’s referring condition.
- Step2: The Research Sweep: In those individuals who are negative in the diagnostic sweep, broadly examine the exome data in order to identify potential pathogenic variants in novel disease genes.

**DIAGNOSTIC SWEEP**

**Phenotypic Categories of Enrolled Participants**
- Mitral Valve Prolapse / Thoracic Aortic Aneurysm, n=7
- Arrhythmia, n=3
- Cardiomyopathy, n=20

**Filter for Pathogenic Variants on Diagnostic Lists**
- MYP / TAA - 14 genes
- Arrhythmia - 14 genes
- Cardiomyopathy - 75 genes

**Diagnostic Yield of WES for Cardiac Patients (%)**

**WES-identified genetic contribution to cardiac disease in NCGENES**

**RESEARCH SWEEP**

Identification of a splice site variant in a Dilated Cardiomyopathy Patient who underwent transplant at age 15 expands the phenotype of SYNE1-associated mutations to include isolated DCM.

- Lymphoblast Cells from DCM patient 24 Exhibit Morphological Changes consistent with disruption of SYNE1, a member of the LINC complex that tethers the nuclear envelope (NE) to the actin cytoskeleton.
- SYNE1 has been shown to be critical for proper mechanotransduction in cardiomyocytes (Banerjee et al., 2014).
- SYNE1 variants have previously been reported in Emery-Dreifuss Muscular Dystrophy (Zhang et al., 2007)

**Whole Exome Sequencing reveals a striking enrichment of rare, truncating variants in nucleoporin genes in cardiac patients**

- WES-identified nucleoporins have a low mutational burden in the ESP cohort.

**WES-Identified NE genes are expressed in the heart**

- Morpholino-based knockdown of WES-identified NE genes leads to cardiac defects in zebrafish embryos, including pericardial edema, and altered looping of the chambers.
- Fahkro et al., 2011 demonstrated L-R patterning defects during Xenopus heart development in nup188 morphants.

**SUMMARY**

WES has Diagnostic Utility for Cardiac Disease, identifying a clearly pathogenic variant in 20% of patients. Alterations in nuclear envelope genes, including nucleoporins, may be particularly important genetic contributors to cardiac disease.