Diagnostic and Research Utility of Whole Exome Sequencing for Cardiac Disease

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- The **N**orth **C**arolina **G**enomic **E**valuation by **N**ext-Generation **E**xome **S**equencing 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**

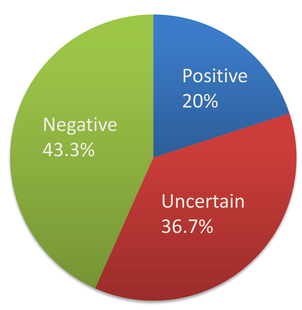
Arrhythmia, **n=3**

Cardiomyopathy, **n=20**

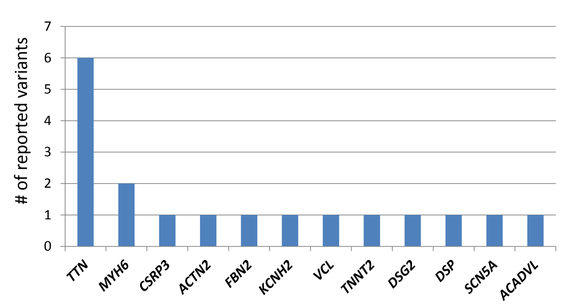
Filter for Pathogenic Variants on Diagnostic Lists

- MVP / TAA - 14 genes
- Arrhythmia - 14 genes
- Cardiomyopathy - 75 genes

Diagnostic Yield of WES for Cardiac Patients (%)

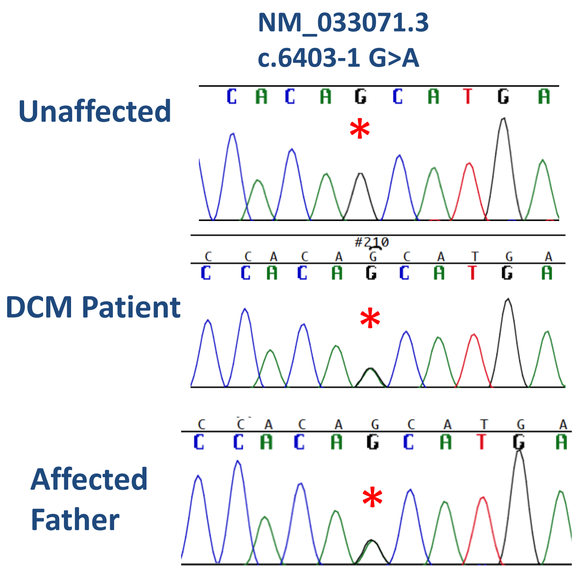


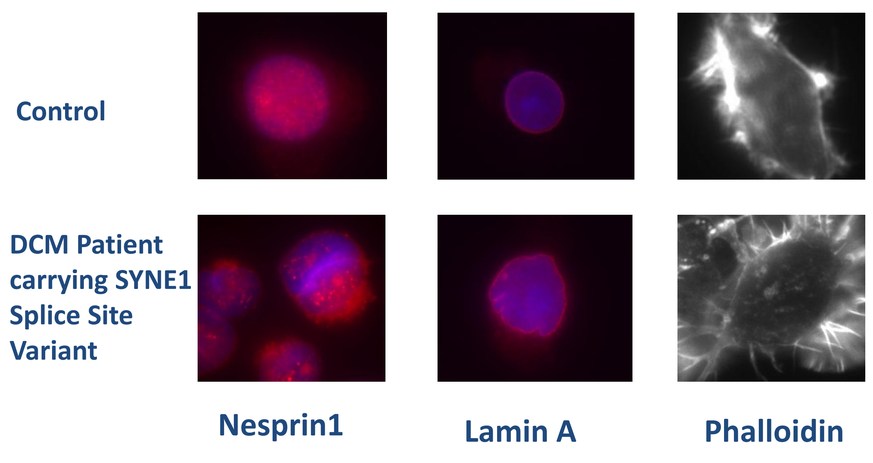
WES-identified genetic contribution to cardiac disease in *NCGENES*



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)

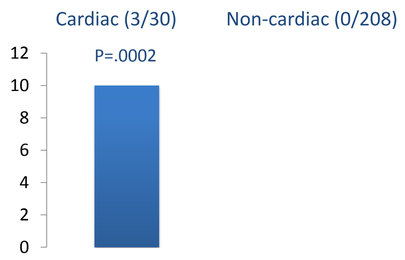
RESEARCH SWEEP

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

Patients with Truncating Variants in Nucleoporins

Patient	Phenotype	Variant	Gene Description	MAF in ESP
96	Arrhythmia; FHx of Sudden Death	NUP37 R106Ter	Nucleoporin of 37kDa	0
157	TAA/MVP; FHx of aneurysms	NUP43 R339Ter	Nucleoporin of 43kDa	.00043
354	TAA/MVP with surgical repair	NUP188 c. 4737+1G>T	Nucleoporin of 188kDa	0

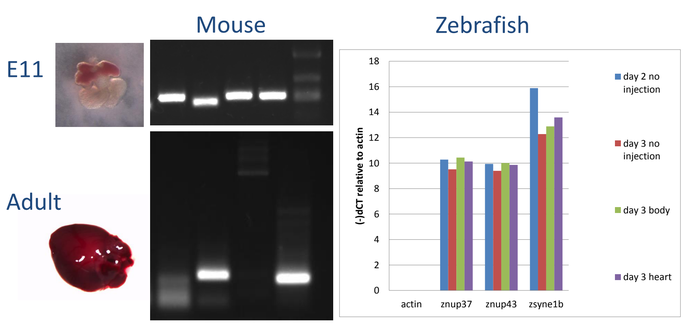
% patients carrying rare, truncating variants in nucleoporins



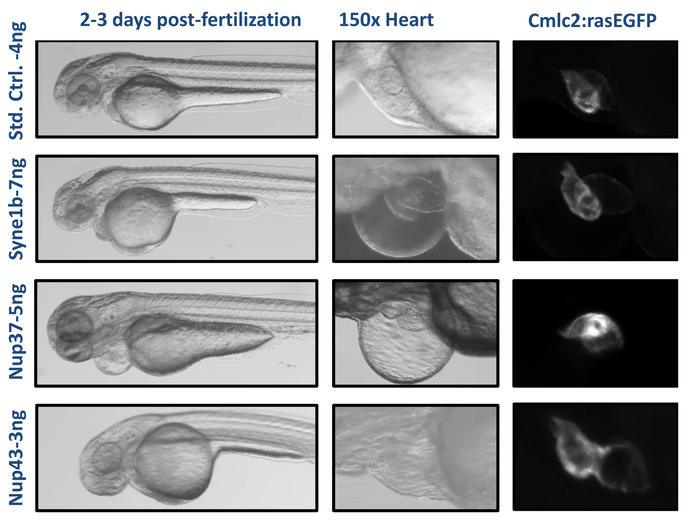
WES-Identified nucleoporins have a low mutational burden in the ESP cohort

Gene	# of coding bases	# of NS variants in ESP	# of Splice-site variants in ESP	% Truncating variants
NUP37	981	0	1	0.001
NUP43	1143	2	0	0.0017
NUP188	5250	0	0	0

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.
- Fakhro et al., 2011 demonstrated L-R patterning defects during Xenopus heart development in nup188 morphants.



NCGenes

North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing

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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.