Escape from genetic purgatory: functional testing of variants of unknown significance

J. Travis Hinson, MD

HINSON LAB @ JAX

Assistant Professor of Genetics and Medicine

The Jackson Laboratory for Genomic Medicine

Director CV Genetics

University of Connecticut Health Center

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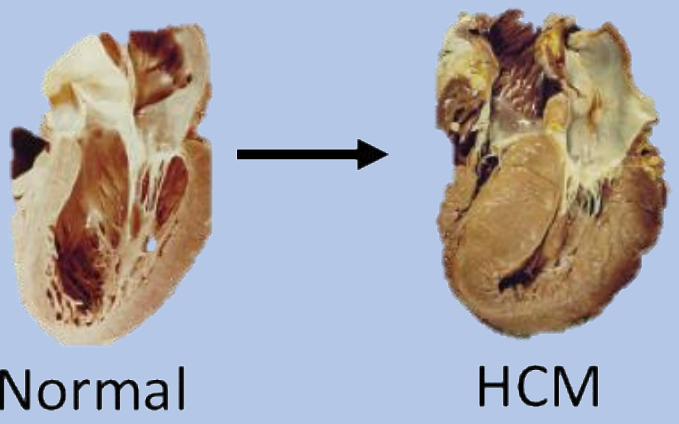
Leading the search for tomorrow's cures

25 year-old man with breathing difficulty during exercise

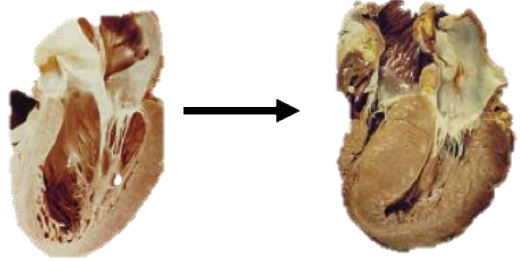
- **Age 17** – He experienced cardiac arrest after basketball practice
  - Resuscitated with CPR provided by a bystander, and a defibrillator shock by EMS.
  - No family history of cardiac arrest or other heart problems
  - Heart ultrasound – Normal heart pump function, but heart walls severely thickened
- **Age 25** – Clinically evaluated for genetic risk with focused cardiomyopathy genetic panel (50 genes tested ; Invitae)
  - Three variants of uncertain significance (VUS) in heart failure-associated genes–*MYBPC3* (Val321Met), *TTN* (Ala17228Val) and *TNNT2* (Pro72His)
  - VUS's are generally not clinically actionable

Hypertrophic cardiomyopathy (HCM)



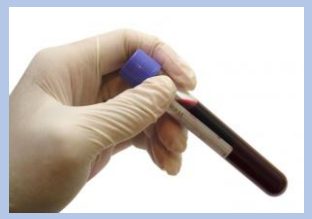
"Disease of the sarcomere"

HCM for the non-clinician

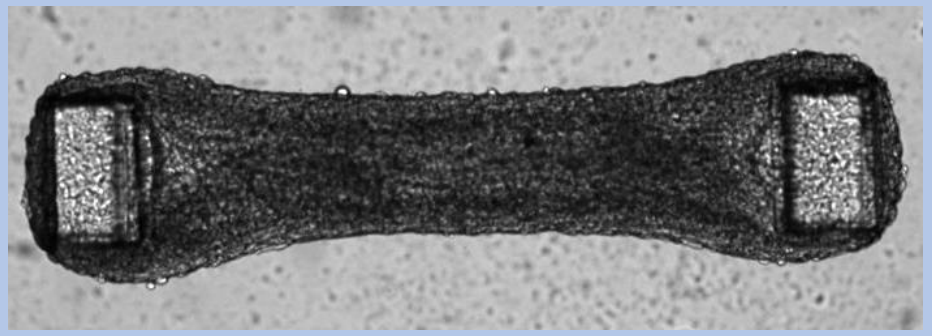


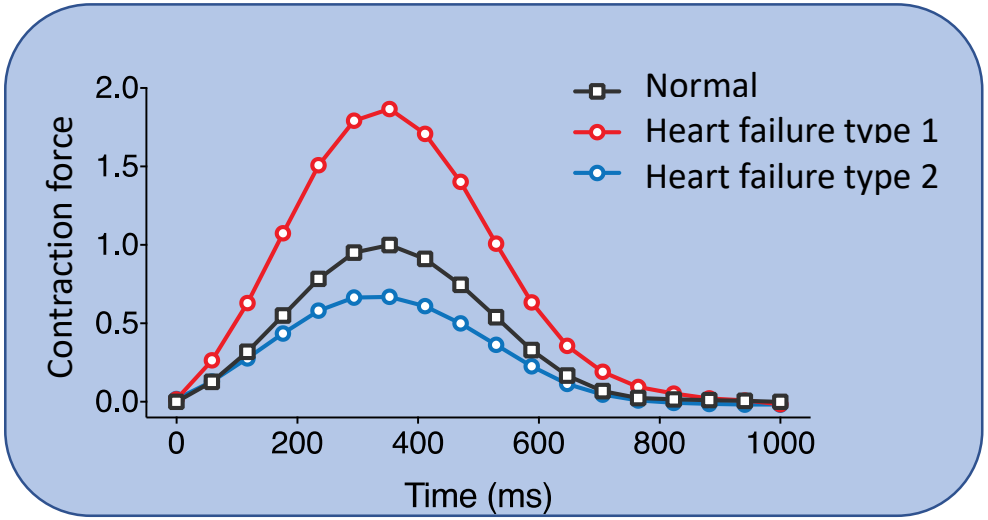
- Prevalence of 1:500 – a common genetic problem
  - ~6,000 individuals in CT alone
- Heart walls are thickened, which impairs heart relaxation
- The major cause of sudden cardiac death in young athletes
- Heart failure is common in adults
- *Genetic disorder* – inherit a single genetic variant from either mother or father (“autosomal dominant”)
  - ”Pathogenic” mutations are identified in ~50% of HCM patients
- Defibrillators reduce the risk of sudden death, and drugs treat symptoms

Human cardiac tissues to study heart failure mutations

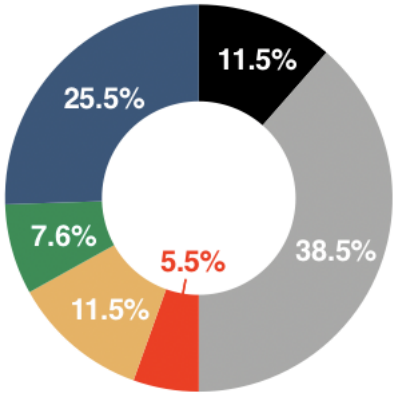


Human cells





Resolving the Variant of Unknown Significance epidemic with human cardiomyocyte assays



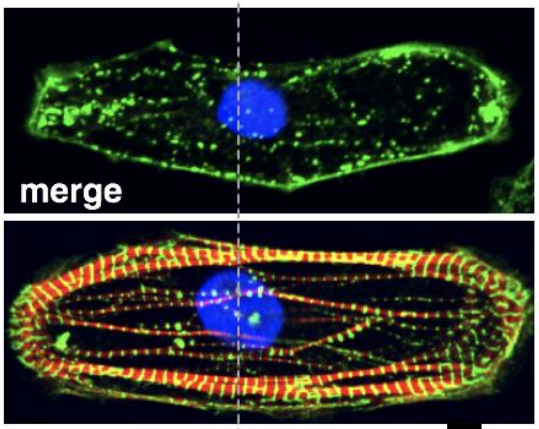
TNNT2 ClinVar Variants (n=384)

- Conflicting interpretations (44)
- Uncertain significance (148)
- Pathogenic (21)
- Likely pathogenic (44)
- Benign (29)
- Likely benign (98)

~50% of *TNNT2* variants are not actionable

Human stem cell-derived cardiomyocyte for functional testing of *TNNT2* variants

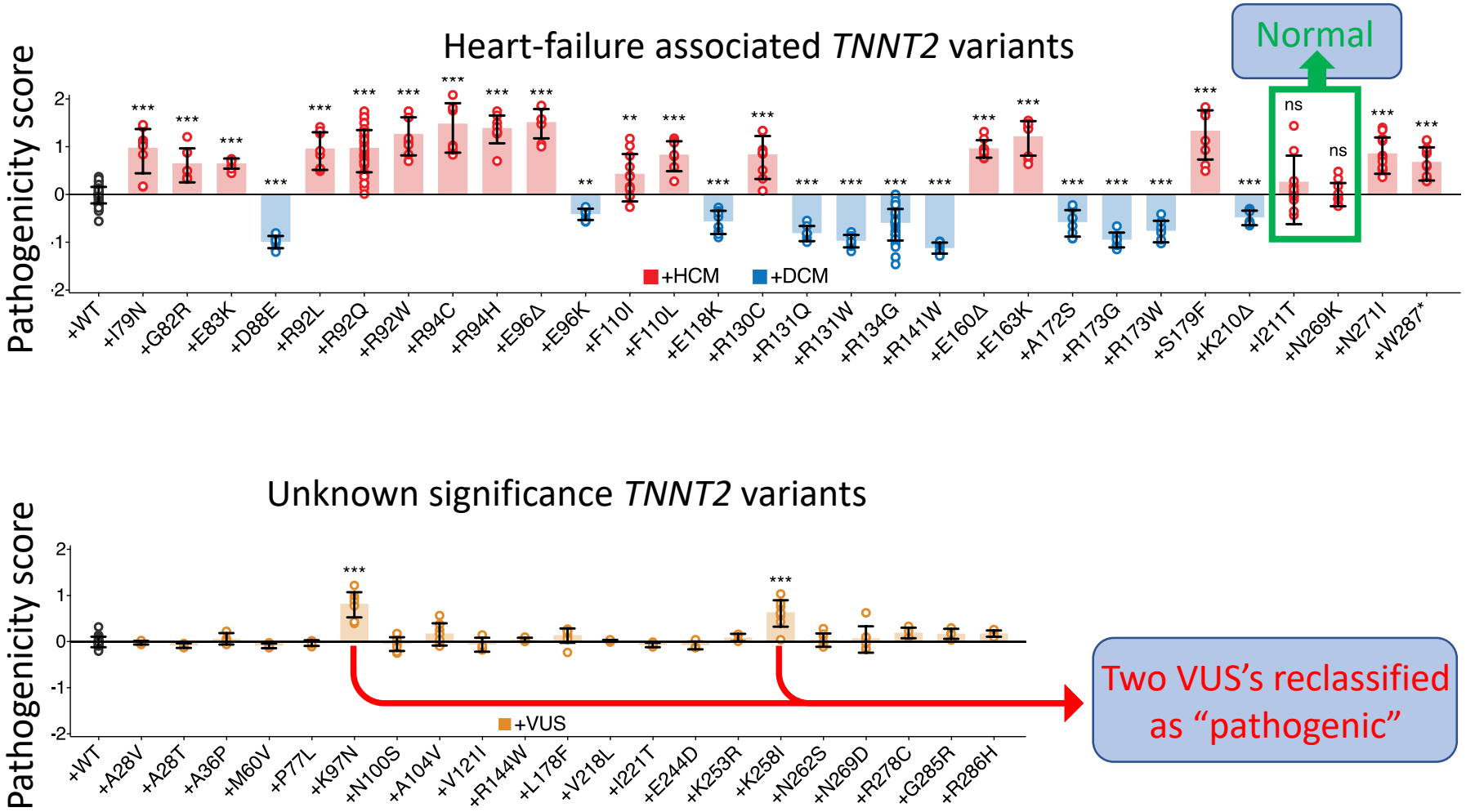
Patient-specific



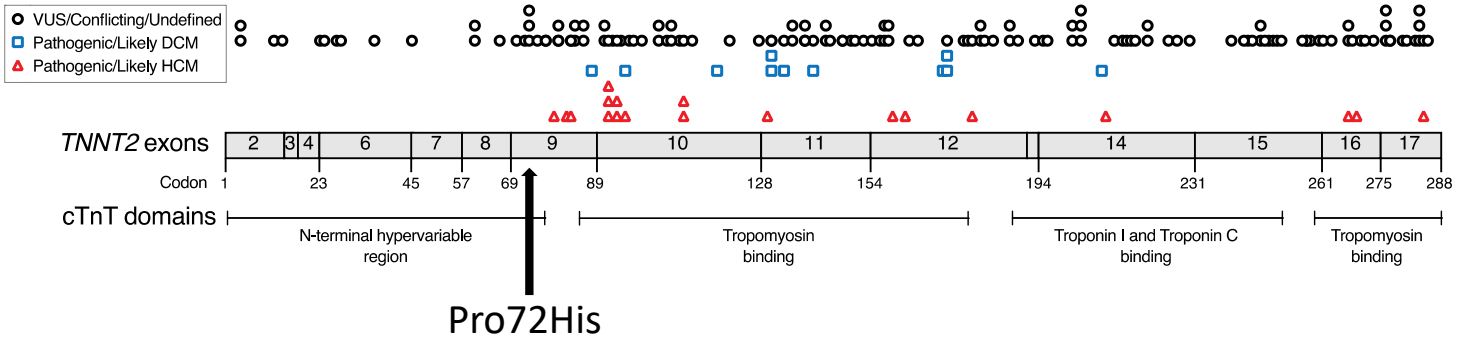
1. Deliver *TNNT2* variants

2. Functional testing in novel assay

Testing a large panel *TNNT2* variants



Back to the patient bedside



Functional testing is in progress but likely benign given location of variant

Treatment plan –

1) Received an implantable defibrillator to prevent death from recurrent cardiac arrest
2) Competitive athletics was recommend against, but moderate exercise was encouraged
3) Family-based genetic testing could not be pursued
4) All siblings, children and parents underwent clinical testing
5) Clinical trials for new HCM therapeutics are underway

Provocative points for discussion

1. While genetic testing is expanding exponentially, we do not understand the function of most genetic variants-> i.e. genetic purgatory

   -How do we approach this from a state level?

   -Centralized committee for genetic testing and interpretation?

2. When should we consider genetic testing for all CT residents?

   -Short term cost -> ~3 million residents – ~$800/person - ~$240 million per year x 10 years (1.3% of annual budget)

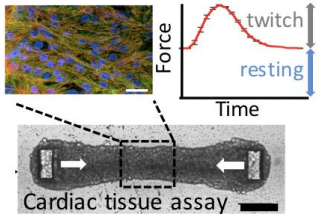
   -Long term -> savings

   -Benefit to patient care

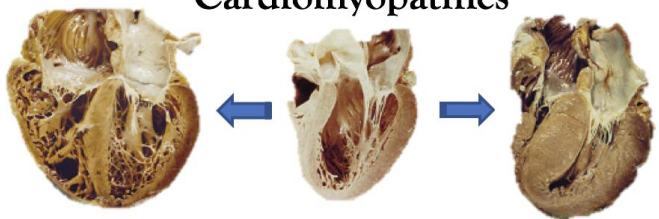
   -Benefit to biomedical research and local industry

   -Provide incentive for industry recruitment

3D Microtissues

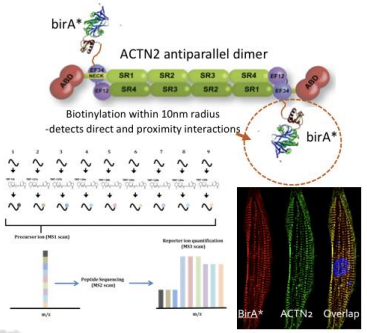


Cardiomyopathies



DCM HCM

Sarcomere BioID



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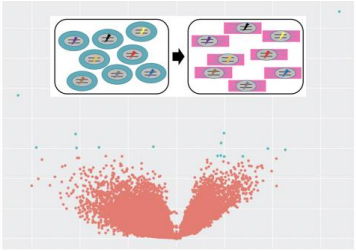
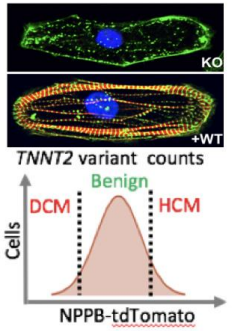
CRISPR screens



The Team

VUS screens



NIH National Heart, Lung, and Blood Institute

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