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

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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

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**Hypertrophic cardiomyopathy (HCM)**

- Normal
- 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

Contraction force

- Normal
- Heart failure type 1
- Heart failure type 2

Time (ms)

Contraction force
Resolving the Variant of Unknown Significance epidemic with human cardiomyocyte assays

~50% of TNNT2 variants are not actionable

1. Deliver TNNT2 variants

2. Functional testing in novel assay

Human stem cell-derived cardiomyocyte for functional testing of TNNT2 variants
Testing a large panel TNNT2 variants

Heart-failure associated TNNT2 variants

Unknown significance TNNT2 variants

Two VUS’s reclassified as “pathogenic”
Back to the patient bedside

Pro72His

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

CRISPR screens

The Team

VUS screens

NIH National Heart, Lung, and Blood Institute

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