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Results from Multigene Panel Testing for 79 Pan-Cardio Genes

BACKGROUND

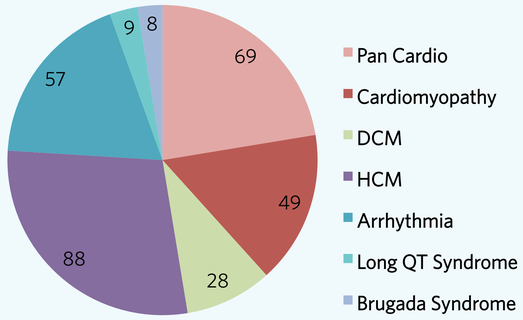
- More than 79 genes have been implicated in multiple cardiovascular diseases including cardiomyopathies, cardiac channelopathies/ arrhythmias and structural heart defects.
- Genetic and phenotypic heterogeneity in cardiovascular disorders make multigene panels an ideal approach to genetic testing.
- We sought to determine the diagnostic yield of testing for 79 cardiovascular genes across 7 panels available for clinical genetic testing from May 2012-June 2013.
- We also sought to determine appropriateness of genes by panel.

METHODS

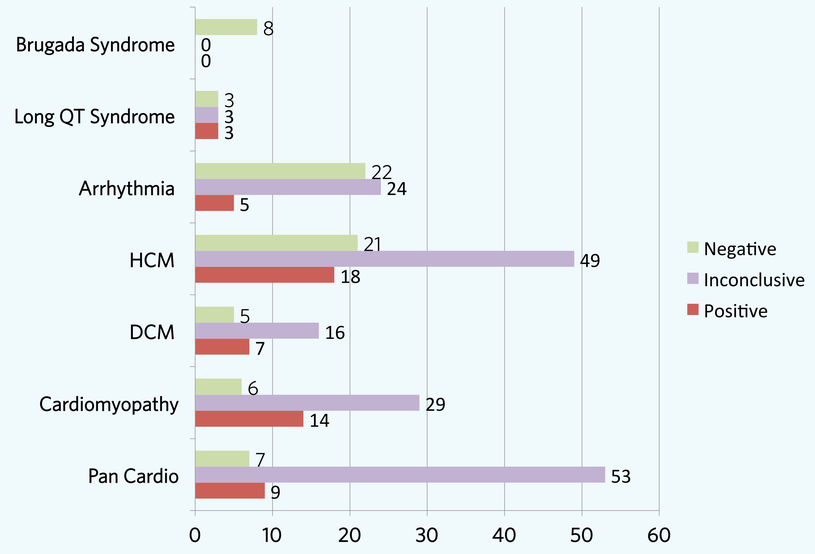
- All probands underwent next generation sequencing
- Sanger sequencing was performed to confirm reported findings and regions with insufficient depth of coverage
- Clinical information was obtained from requisitions submitted by clinicians

Cohort (N=308)

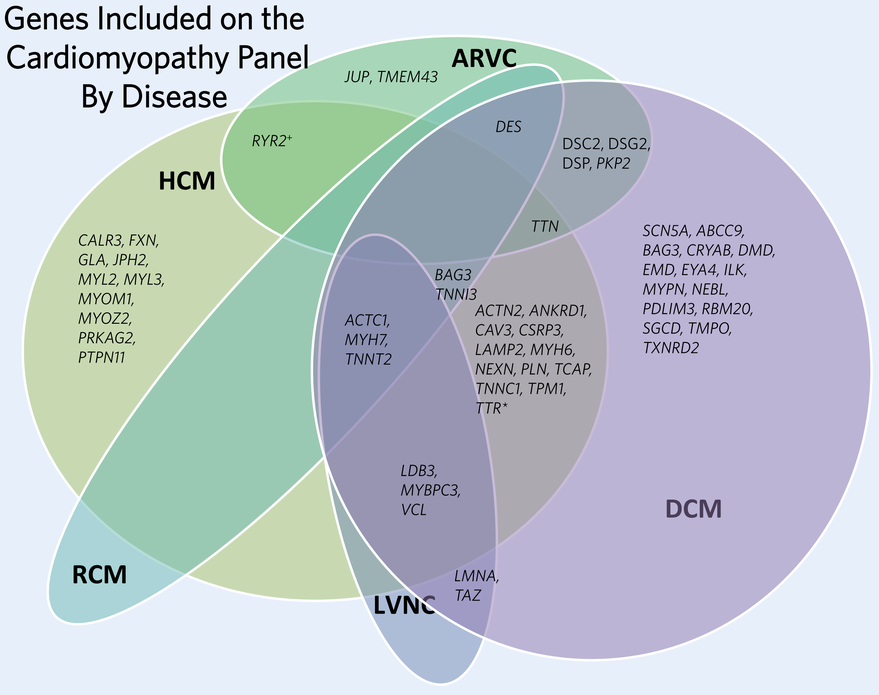
Total Cases Submitted



Proportion of cases yielding positive results



Genes Included on the Cardiomyopathy Panel By Disease



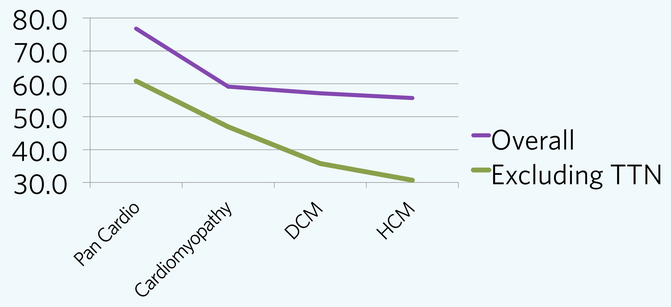
Syndromic Cases

- Probands with syndromic features had pathogenic alterations diagnostic of the specific syndrome.
- Examples include:
  - *PTPN11* mutation diagnostic in an infant with features of Noonan's syndrome
  - *GLA* mutation in a patient with Fabry Disease
  - *EMD* mutation in a patient with cardiomyopathy and skeletal muscle weakness

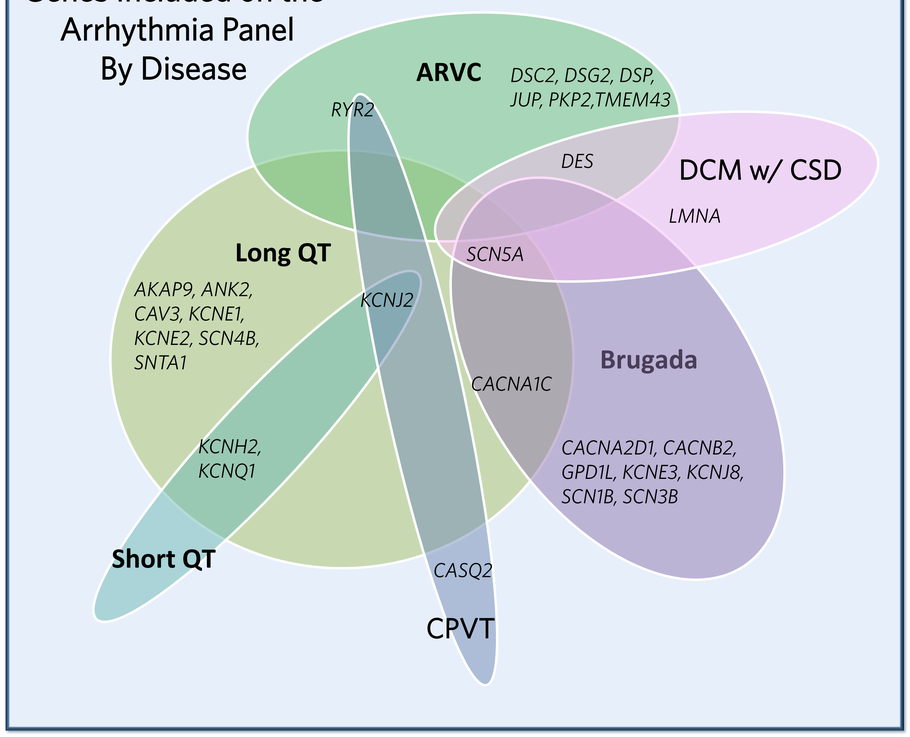
Alterations in Titin (*TTN*)

- *TTN* included in testing for 234 probands, as mutations have been correlated with DCM & HCM; however, rare missense variants in *TTN* are common in the general population.
- 7 pathogenic alterations were reported in *TTN* across Pan Cardio, Cardiomyopathy, DCM & HCM panels, accounting for 11%, 28%, 29% and 0% of positive cases, respectively.
- 57.6% of overall cases resulted in inconclusive results, with one or more VUS detected.
- **40.8% of all VUS were attributed to *TTN* missense variants.**
- The burden of VUS in *TTN* should be weighed with the additional yield of positive results

Percentage of Overall Results Reported as Inconclusive



Genes Included on the Arrhythmia Panel By Disease



Gene Alterations Reported

- A pathogenic/likely pathogenic alteration was identified in the following 26 genes (33.0%):
  ANK2(1), BAG3(2), DSG2(1), DSP(2), EMD(1), FXN(1), GLA(1), KCNE1(2), KCNH2(2), KCNQ1(2), LMNA(2), MYBPC3(13), MYH7(9), MYL3(1), MYOM1(1), PKP2(1), PLN(1), PTPN11(2), RYR2(1), SCN3B(1), SCN5A(2), TMEM43(1), TNNI3(1), TNNT2(2), TTN(7), TTR(2)
- Overall, a pathogenic/likely pathogenic alteration was identified in 19.4% (60/308) of cases
  - Pan Cardio: 18.8% detection rate
  - The detection rate for pathogenic alterations in genes included on the HCM (20%) and DCM (25%) panels were lower than those reported in the literature (40%-60%), possibly due to the high stringency of our classification criteria for clinical significance.
- At least one VUS was identified in 65 genes (82.3%)
- No alterations with potential clinical relevance were reported in the following 14 genes (17.7%):
  CAV3, CRYAB, GATA4, JAG1, JUP, KCNE3, KCNJ2, NKX2.5, PRKAG2, SCN4B, SGCD, TAZ, TCAP, TNNC1

TAKE-HOME POINTS

- The high mutation detection rate from our cohort demonstrates the inherent value of multigene Pan-Cardio panels, though targeted gene analysis may be most appropriate for clearly syndromic conditions.
- Limiting the assessment of *TTN* to probands with a history of DCM should be considered to limit the VUS burden on clinical interpretation while targeting the most appropriate populations for testing.
- Those genes in which no clinically relevant alterations were detected should be re-evaluated for utility of inclusion.