SUPPLEMENTAL MATERIAL

Interpretation of incidental genetic findings localizing to genes associated with cardiac channelopathies and cardiomyopathies

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Supplemental Materials

Supplemental Table I:

Summary of ACMG-identified clinically actionable/reportable genes

Disease	Actionable/Reportable Genes*
Hypertrophic Cardiomyopathy	*ACTC1*†, *GLA, MYBPC3*†, *MYH7*†, *MYL2, MYL3, PRKAG2, TNNI3*†, *TNNT2*†, *and TPM1*†
Arrhythmogenic Right Ventricular Cardiomyopathy	*DSG2, DSP, DSC2, PKP2, and TMEM43*
Dilated Cardiomyopathy	*ACTC1*†, *LMNA, MYBPC3*†, *MYH7*†, *TNNI3*†, *TNNT2*†, *and TPM1*†
Catecholaminergic Polymorphic Ventricular Tachycardia	*RYR2*
Long QT Syndrome	*KCNQ1, KCNH2, and SCN5A*‡
Brugada Syndrome	*SCN5A*‡

*Based on 2013 ACMG guidelines on reporting of incidental findings in exome and genome sequencing[6-8]. †Genes overlap between HCM and DCM disease phenotypes. ‡, Gene overlap between LQTS and BrS disease phenotypes.

Supplemental Table II:
Prevalence, frequency, and signal-to-noise ratios of variants associated with inherited cardiac channelopathies and cardiomyopathies.

Disease	Disease Prevalence	Variant/Variant Frequency				Signal:Noise			Incidental Variant Prevalence vs Disease Prevalence*		Ref
		Pathogenic	Population	Incidental LP/P	Incidental VUS	Pathogenic: Population	Incidental LP/P: Population	Incidental VUS: Population	Incidental LP/P: Prevalence	Incidental VUS: Prevalence	
Hypertrophic cardiomyopathy	1 in 500	50%	5%	0.5%	6.8%	10:1	0.1:1	0.41:1	2.5-fold	34-fold	24-28
Arrhythmogenic right ventricular cardiomyopathy	1 in 5000	60%	16%	0.4%	14%	3.8:1	0.025:1	0.0875:1	20-fold	700-fold	29-30
Dilated cardiomyopathy	1 in 2500	30%	14%	N/A	N/A	2.14:1	N/A	N/A	N/A	N/A	31-35
Catecholaminergic polymorphic ventricular tachycardia	1 in 10,000	47%	6%	0.2%	9%	8.3:1	0.033:1	1.5:1	20-fold	900-fold	36-38
Long QT syndrome	1 in 2000	75%	10%	0.5%† 1.2%‡	11%† 37%‡	7.5:1	0.05:1† 0.12:1‡	1.1:1† 3.7:1‡	10-fold† 24-fold‡	220-fold 740-fold‡	39-41
Brugada syndrome	1 in 2,000	21%	5%	0.3%	6.3%	4.2:1	0.06:1	1.26:1	6-fold	126-fold	40,42

Variant frequency for each disease is based on variant classification. Pathogenic percentage denotes individuals positive for a pathogenic variant in one of the genes associated with disease. Population variants are rare variants found in a large population cohort. LP/P, incidentally identified likely pathogenic and/or pathogenic variants. N/A, not available or not identified. *Fold-difference between the prevalence of incidentally identified variants versus known disease prevalence in the community. Calculation based on presumption that all individuals with disease are genotype positive. †Only ACMG-designated actionable genes associated with LQTS (*KCNQ1, KCNH2, and SCN5A*), ‡All LQTS-associated genes