Condition Proportions and Genetic Testing Utilisation and Yield in their Investigation at an Inherited Cardiac Conditions Clinic

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Introduction

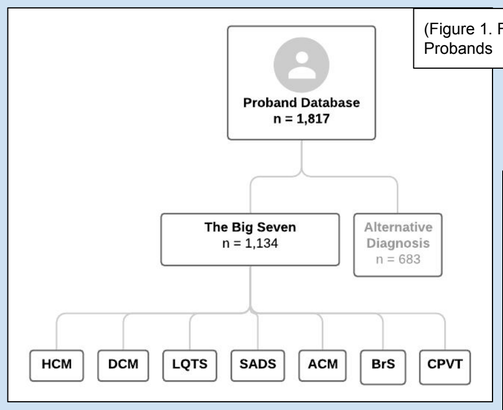
The Family Heart Screening Clinic (FHSC) in Dublin's North Inner City is a facility for the detection and management of Inherited Cardiac Conditions (ICCs) in at-risk families. This study was undertaken to compare the proportions of conditions referred/detected within the proband subgroup of patients at the FHSC and assess the uptake and yield of genetic testing in the probands.

Methods

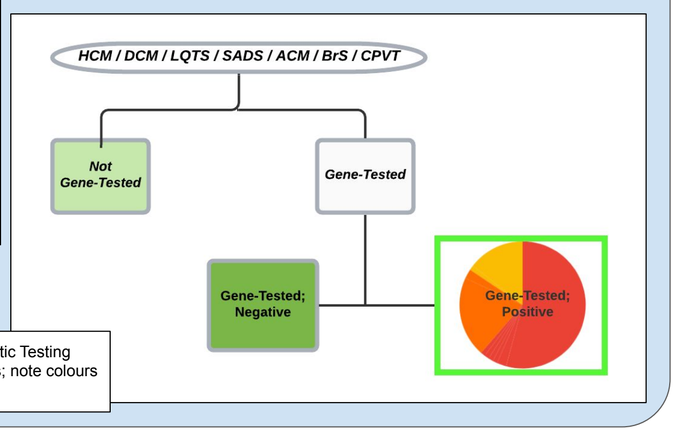
In this retrospective study, we interrogated the FHSC proband database. A proband is the individual acting as a starting point for the genetic study of a family. This database numbered 1,817 individuals (representing a total of 3,316 *condition-affected* persons) in July 2020. We extracted data about the probands whose primary diagnosis was one of seven ICCs: Hypertrophic Cardiomyopathy (HCM; n=444), Dilated Cardiomyopathy (DCM; n=235), Long QT Syndrome (LQTS; n=223), Sudden Adult Death Syndrome (SADS; n=165), Arrhythmogenic Cardiomyopathy (ACM; n=30), Brugada Syndrome (BrS; n=25) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT; n=12) (see Figure 1.).

We then subdivided the probands within each condition group into three further subgroups for comparison with regard to their genetic testing status: firstly, those not genetically tested; secondly, those whose genetic testing was negative; thirdly, those who had a finding of a genetic variation on genetic testing (see Table 1.). For the purposes of this undertaking we included the pathogenicity classifications of Pathogenic (P), Likely Pathogenic (LP) and Variants of Uncertain Significance (VUS) by American College of Medical Genetics (ACMG) Classification Standards as *not negative* genetic findings.

Finally, we tallied the relative proportions of P, LP and VUS classification for each condition (see Figures 3.-8.).



(Figure 1. Flow-charts demonstrating Selection of our Relevant Probands

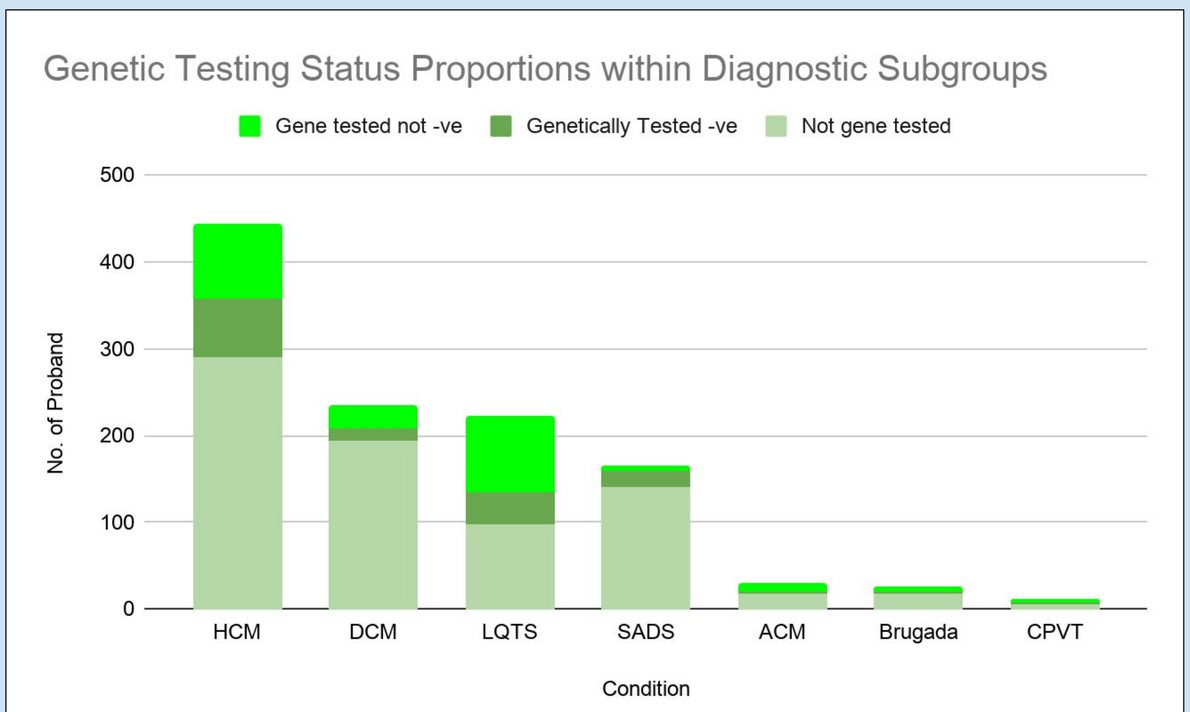


(Figure 2. Flow-charts demonstrating Genetic Testing Uptake and Yield of our Relevant Probands; note colours which correspond to bar chart)

Results

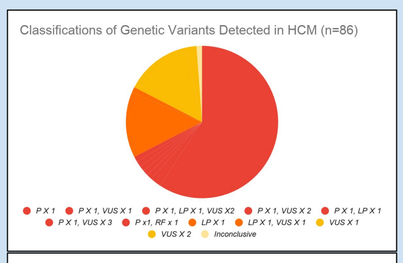
Condition	n=	No Genetics	Genetics	Genetics -ve	Genetics not -ve	Pathogenic*	Likely Path*	VUS*	> 1 variant
HCM	444	290 (65.3%)	154 (34.7%)	68 (44.2%)	86 (55.8%)	58 (67.4%)	13 (15.1%)	14 (16.3%)	10
DCM	235	193 (82.1%)	42 (17.9%)	15 (35.7%)	27 (64.3%)	9 (33.3%)	11 (40.7%)	7 (25.9%)	5
LQTS	220	98 (44.5%)	122 (55.5%)	37 (30.3%)	85 (69.7%)	51 (60%)	21 (24.7%)	13 (15.3%)	9
ACM	30	17 (56.7%)	13 (43.3%)	3 (23%)	10 (77%)	6 (60%)	1 (10%)	3 (30%)	1
BrS	25	18 (72%)	7 (28%)	2 (28.6%)	5 (72.4%)	2 (40%)	3 (60%)	0 (0%)	0
CPVT	9	6 (66.7%)	3 (33.3%)	1 (33.3%)	2 (66.7%)	2 (100%)	0 (0%)	0 (0%)	0
SADS	165	140 (84.8%)	25 (15.2%)	18 (72%%)	7 (28%) ^	0 (0%)	0 (0%)	7 (100%)	0
Total	1128	762 (67.6)	366 (32.4%)	144 (39.3%)	222 (60.7%)	128 (57.7%)	49 (22.1%)	44 (19.8%)	25

(Table 1. Genetic Testing Status)



(Figure 3. Genetic Testing Status Proportions within Diagnostic Subgroups)

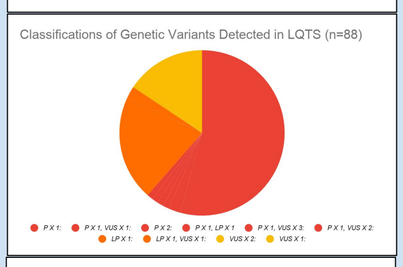
Tallying of variant pathogenicity classifications within the gene *not negative* subgroup for the conditions revealed the following proportions of pathogenicity (see Figures 3.-8.). For these figures, colours were applied based on *highest* pathogenicity classification present when there were multiple variants found in one sample.
ACMG Classification of Variants Detected, Figures 4.-9. :
Red - Pathogenic variant; Orange - Likely Pathogenic Variant; Yellow - Variant of Uncertain Significance



(Figure 4. *Classifications of Genetic Variants Detected in HCM (n=86)*)

P or LP: 83.5%

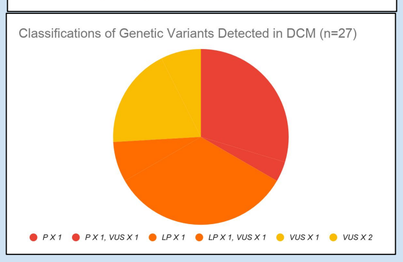
VUS: 16.5%



(Figure 5. *Classifications of Genetic Variants Detected in LQTS (n=88)*)

P or LP: 85.2%

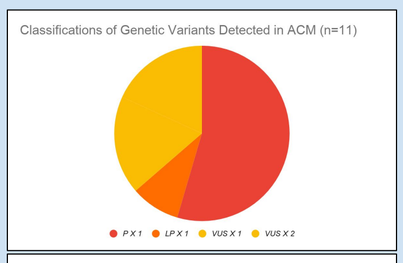
VUS: 14.7%



(Figure 6. *Classifications of Genetic Variants Detected in DCM (n=27)*)

P or LP: 74.1%

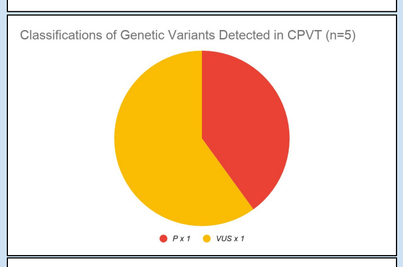
VUS: 25.9%



(Figure 7. *Classifications of Genetic Variants Detected in ACM (n=11)*)

P or LP: 63.7%

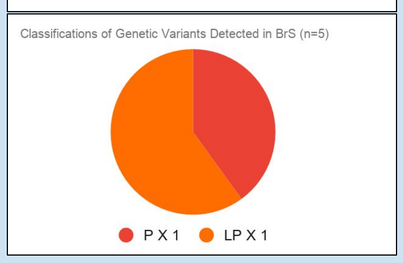
VUS: 36.3%



(Figure 8. *Classifications of Genetic Variants Detected in CPVT (n=5)*)

P or LP: 40%

VUS: 60%



(Figure 9. Classification of Genetic Variants Detected in BrS (n=5))

P or LP: 100%

VUS: 0%

Discussion

The interface between clinical and genetic investigation is a rapidly evolving area. The expanding information base is slowly classifying each variant detected based on phenotypes associated with that variant. Variable penetrance and expressivity of these variants allows for significant clinical heterogeneity in some cases eg. LQTS while other variants have more homogenous associated phenotypes eg. HCM.
SADS diagnoses are a special case in the clinical phenotype-genotype interface because the phenotype cannot be investigated clinically. Autopsy findings and the cardiac arrest event may be the only available phenotypic evidence of a possible ICC. A SADS death may become a SCD within one of our other categories if molecular autopsy reveals pathogenic mutation. This meant that 10 SADS cases who had *not negative* molecular autopsies were moved to LQTS (n=5; LP, LP, VUS, VUS, VUS), CPVT (n=4; P, VUS, VUS, VUS), and ACM (n=1, VUSx2) in the course of this study.
In clinical practise a VUS is non-actionable and these aforementioned VUS cases would remain in the SADS category. There is not always clear consensus on at what point a deceased person may be considered a SADS death or death secondary to these conditions even with molecular autopsy.
VUSs are not typically considered actionable findings in clinical practise. They are defined by ACMG as VUSs as there is not currently a sufficient evidence base as to their effects. Publication of findings regarding VUSs should be published so as to build the evidence base and tease out the pathogenicity or benignness of these variants.
Genetic testing is commonly used for genetic confirmation of a clinical diagnosis and co-segregation of at-risk family members accordingly.
The importance of genetic testing in the clinic is not limited to guiding management of a patient. While a diagnosis of an ICC in one family member identifies a family as at-risk, a not negative genetic diagnosis of one family member allows for stratification of other family members. A gene negative family member of a gene not negative proband may be reassured and removed from the at-risk category.
Testing is also useful where features of disease have not yet become apparent eg. early HCM and where day-to-day variation in features eg. QT duration in LQTS or intermittent nature of events eg. CPVT may escape the detection of clinical testing.

The frequencies of presentation may be used to inform oversight at this ICC clinic. As well as informing external clinicians as to the most prevalent conditions being managed in this Irish ICC setting.

Conclusions

The overall utilisation of genetic testing was relatively low at 32.4% in this cohort. The overall *not negative* (P, LP or VUS) rate for genetic testing across the ICCs probands in whom genetic testing was pursued was 60.7%. Combined P / LP variant rates within the *not negative* group in the larger cohorts of HCM (n=86) and LQTS (n=88) were 82.5% and 84.7% respectively. VUS rates vary from 0% to 30% within the *not negative* groups (excluding SADS where it was 100%). Factors contributing to low rates of genetic testing and phenotypic predictors of positive genotype warrant further investigation.

VUSs are a significant minority of findings on genetic testing. ACMG guidelines recommend that VUSs not be used in clinical decision making and that efforts should be made to resolve the classification to 'pathogenic' or 'benign' - by publishing findings and seeking others' publications about the same. ACMG recommends that patients avail of additional monitoring in the meantime.