THE GENOMIC MEDICINE FOUNDATION (UK)
FELLOWSHIP, SCHOLARSHIP, EDUCATION AND PROMOTION OF GENOMIC APPLICATIONS IN MEDICINE, HEALTHCARE AND SOCIO-ECONOMIC PROGRESS

The IX International Conference of Cardiovascular Genomic Medicine
Royal College of Surgeons, Edinburgh, Scotland
23-24 October 2023

The next (9th) **Biennial International Cardiovascular genomics conference** is held on 23-24 October 2023. The main theme of this conference is '***Precision Cardiovascular Medicine'***. The scientific programme, delivered by leading global experts, includes the ***Third William Harvey Oration***, plenary/ key-note lectures, and scientific oral & poster sessions.

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Prof. Christopher Semsarian (University of Sydney, Australia)

Programme

Theme: "PRECISION CARDIOVASCULAR MEDICINE"

Day 1 Monday 23rd October 2023

0800 **Reception/ Registration**

0900 **Welcome/ Introduction**
Professor Dhavendra Kumar, William Harvey Research Centre, Bart's Medical School, QMUL, UK
d.kumar@qmul.ac.uk

0915- 1115 **Session I: Diagnostic cardiovascular genomics**
Chair- Professor Mary Porteous, Clinical Geneticist, Edinburgh, Scotland
Mary.porteous@ed.ac.uk

1. Dr. Lorenzo Monserrat, Naevia Medical, La Coruna, Spain
'*Genomic evolution of diagnostic cardiology*'
lorenzo.monserrat@naeviamedical.com

2. Prof. James Ware, Imperial, London
'Genotype/phenotype in inherited cardiovascular conditions: do genomic biomarkers yield clinically-useful predictions?'
j.ware@imperial.ac.uk

1115 ***Coffee break***

1130-1330 **Session II: Genotype-Phenotype ontology in cardiovascular genomics**
Chair: Dr. John Dean, Clinical Geneticist, Aberdeen, Scotland
John.dean@nhs.scot

3. Dr. Farrah Khawaja, Deputy Director of Genomics Quality Assessment (GenQA), Royal Infirmary of Edinburgh, Scotland, UK.
'*Challenges of genome diagnosis in clinical cardiology*'
Farrah.khawaja@genqa.org

4. Dr. Verity Harthill, Leeds Institute of Medical Research, University of Leeds, St James University Hospital, Beckett Street, Leeds, UK
'Understanding the genetic basis of congenital heart disease; whole genome sequencing opens new avenues for investigation, but significant challenges remain'
Verity.hartill@nhs.net

1330- 1430 ***LUNCH***

1430- 1500 **Session III: Posters viewing**

1500-1600 **Session IV: 'Multi-OMICS Cardiovascular Medicine'**
Chair- Prof. Martin Denvir, Cardiologist, Edinburgh, Scotland
martin.denvir@ed.ac.uk

5. Prof. Seema Mital, Hospital for Sick Children, Toronto, Canada
"A multi-omics approach to diastolic heart failure"
Seema.mital@sickkids.ca

6. Dr. Anna Maria Choy, Cardiologist, Univ. Dundee, Scotland
' Multi-disciplinary management of arrhythmia syndromes'
a.choy@dundee.ac.uk

1600-1630 ***TEA***

1630-1730 **Session V: Cardiovascular genomic precision medicine- back to the future'**
Key Note Lecture: Chair- Prof. James Ware, Imperial College, London.
j.ware@imperial.ac.uk

7. Prof. Perry Elliott, UCL, London, UK
'*Emerging novel treatment prospects for cardiomyopathies'*
Perry.elliott@ucl.ac.uk

1730 **Panel discussion- Reflections of the Day**
CLOSE OF DAY 1

1930 ***Scottish Reception/ Welcome***
2000 ***Conference Dinner (Smart casual / Traditional/ National)***

Day 2 Tuesday 24th October 2023

0830-0930 **Reception/ Registration**

0930-1015 **Key note lecture, Chair: Prof. Dhavendra Kumar**

8. Prof. Sir Munir Pirmohamed, Universtity of Liverpool, UK
'Pharmacotherapy cardiovascular genomic medicine'
Munirp@liverpool.ac.uk

1015-1130 **Session VI: 'Oral Award presentations (10 minutes each with 5 minutes Q/A & Discussion)**
Chairs: Dr. Caroline Coats, Cardiologist, Glasgow
caroline.coats@ggc.scot.nhs.uk

Dr. Ruth McGowan, Clinical Geneticist, Glasgow, Scotland.

ruth.mcgowan@ggc.scot.nhs.uk

Judges: Dr. Wayne Lam, Edinburgh, Scotland; Dr. Catherine Mercer, Southampton, England; Dr. Siv Fokstuen, Geneva, Switzerland.
Wayne.lam@ed.ac.uk ; Catherine.mercer1@nhs.net ; Siv.Fokstuen@hcuge.ch

*1. '***Double Trouble in the hypertrophic heart'**
A. Kissopoulou, Department of Cardiology, County Hospital-Ryhov, Jönköping, 55185, Sweden
antheiakissopoulou@yahoo.com ; antheia.kissopoulou@rjl.se

2. '**One test, a lifetime of precision familial hypercholesterolemia reports',** Aditi Babel, Imperial College Healthcare NHS Trust, London, UK
Adt.babel@gmail.com

3. 'Distinct signaling events from the overexpression of the PRKAG2 R302Q variant of AMPK lead to Hypertrophic phenotype'
Vanya Vaidya, Department of Cardiology, PGIMER, Chandigarh, India
vanyavaidya@gmail.com

4. 'WGS analysis reveals an Alu retrotransposon element insertion in the *NEXN* gene confirming a diagnosis of paediatric onset autosomal recessive dilated cardiomyopathy (AR DCM) in a family'
Mary Gable, Bristol Genetics Laboratory/South West Genomics Laboratory Hub, Southmead Hospital, Bristol, England, UK
Mary.gable@nbt.nhs.uk

5. 'Prediction of Atrial Fibrillation using Polygenic Risk Scores for Cardiovascular Risk Factors'
Julia Ramirez, Aragon Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain; Centre of Clinical Pharmacology and Precision Medicine, William Harvey Research Institute, Queen Mary University of London, U.K
j.ramirez@qmul.ac.uk

1130 COFFEE

1145-1315 Session VII 'Genomic precision cardiovascular medicine
Chair: Prof. Sandi Deans, University of Edinburgh, Scotland
Sandi.deans@ed.ac.uk

10. Prof. Nimesh Desai, Cardiovascular Surgery, University Pennsylvania, Philadelphia, USA
'Genotype driven surgical management of aortopathies'

Nimesh.desai@pennmedicine.upenn.edu

11. Prof. Sandosh Padmanabhan, Glasgow, Scotland, UK
'Genomics and the cardiovascular continuum'
Sandosh.padmanabhan@glasgow.ac.uk

12. Dr. William Young, Bart's Heart Centre, Bart's Hospital & Queen Mary University of London, UK
'*Molecular autopsy in sudden cardiac death'*
William.young1@nhs.net

1315-1430 ***LUNCH/ POSTERS***

1430-1600 **Session VIII: Personal genomics in preventive cardiology**
Chair: Prof. Sandosh Padmanabhan, University of Glasgow
Sandosh.padmanabhan@glasgow.ac.uk

13. Prof. Manuel Mayr, Imperial College, London.
' Cardiovascular proteomics of coronary artery disease'
m.mayr@imperial.ac.uk

14. Prof. Panagiotis Deloukas, Queen Mary University, London.
'Polygenic scoring systems in preventive cardiology'
p.deloukas@qmul.ac.uk

15. Prof. Patricia Munroe, Queen Mary University, London
'*Complex genomics of systemic hypertension'*
p.b.munroe@qmul.ac.uk

1600-1630 ***TEA***

1630-1730 **'The Third William Harvey Oration'**
Facilitator- Professor Sir Munir Pirmohamed
munirp@liverpool.ac.uk

17. Invited speaker- Prof. Arthur A.M. Wilde, University Amsterdam,
'Evolution of channelopathies in clinical cardiology'
a.a.wilde@amsterdamumc.nl

1730 **Reflections of the Day ; Best Oral and Poster presentations awards**
Vote of Thanks- *Close and Bon Voyage*

All enquiries to-
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d.kumar@qmul.ac.uk ; md@genomicmedicine.org ; genomicmedicine@yahoo.co.uk

Mr. Nicholas Miles- Events Manager, Neon Events, Cardiff, UK- nick@neon-events.co.uk

Poster presentations: (see Abstracts folder)

1. Identification of a novel founder nonsense variant in *DSP* causes Familial Cardiomyopathy in Multiplex Arabian Consanguineous Family with Four Affected Siblings

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Abstract

Introduction: Familial dilated cardiomyopathies (DCM) are a heterogeneous group of diseases that often have a genetic cause, and can lead to arrhythmia, heart failure and sudden death. Familial DCM is diagnosed when two or more family members meet the criteria for DCM. **Methods**: a multiplex family with four affected daughters all having familial DCM. Autozygosity mapping and exome sequencing was conducted in the two of the affected siblings (the other two were deceased) followed by segregation analysis. Echocardiographic findings showed arrhythmogenic right ventricular cardiomyopathy. **Results:** Autozygosity mapping confirmed the two affected individuals shared IBD across the *DSP* gene (encoding Desmoplakin) locus at Chr 6. Analysis of exome data interestingly led to identification of homozygous nonsense mutation (c.4297C>T; p.Gln1433*) rs1554108283 in exon 23 of *DSP* gene. It is a loss-of-function mutation that predicts a premature termination of translation. The parents are heterozygous carriers for the mutation which confirms the mutation is segregated with the disease phenotype. Remarkably, according to ACMG guidelines this mutation is classified as pathogenic. However, it is not cited in any genome browsers up to date. **Conclusion:** we reported a rare novel pathogenic nonsense variant causing desmosomal familial DCM in multiplex Arabian family with four affected siblings.

Keywords: Familial dilated cardiomyopathies; *DSP* gene; Consanguinity, sudden cardiac death

2. Double Trouble in the hypertrophic heart

A.Kissopoulou[1], L.Guthreau[1], T. Stumpf[1], C.Gunnarsson[2]
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Introduction: Cardiac amyloidosis and hypertrophic cardiomyopathy are associated with increased left ventricular wall thickness. Differential diagnosis of these entities can be challenging. To our knowledge, this is the first reported case of a patient with hereditary cardiac amyloidosis and hypertrophic cardiomyopathy.
Case presentation: A 45-year old man, from Nigeria was diagnosed with hypertrophic cardiomyopathy in 2000 when he experienced syncopal episodes during running. Echocardiography revealed a hypertrophied septum around 24mm without any outflow obstruction. He received an ICD and had several appropriate ICD discharges in 2014. No arrhythmias were noticed after increasing the beta-blocker. Regarding his family history, his father died suddenly at the age of 55 during exercise and his younger sister has sought for palpitations. Genetic testing performed in 2022 detected two pathogenic variants: one heterozygote in **MYPBC3(c3330+5G>C)** associated with familial hypertrophic cardiomyopathy and a heterozygote in **TTR(c.424G>A p.(Val142Ile))** that has been reported to cause cardiac amyloidosis. This variant is found in 3.5% of African Americans and is defined as a late-onset cardiac amyloidosis. New echocardiography depicted a more pronounced concentric hypertrophy of the left ventricle, with some septal dominance. Cardiac technetium-99m pyrophosphate scintigraphy strongly suggested transthyretin amyloidosis. No peripheral nervous system involvement was noticed. Taking into account that our patient had obvious signs of cardiac amyloidosis, he received tafamidis, an amyloid stabilizer and keeps doing well.
Conclusion: Hereditary transthyretin cardiac amyloidosis and hypertrophic cardiomyopathy can co-exist. This case illustrates the importance of genetic testing to clarify the diagnosis of cardiac hypertrophy and its impact on therapeutic options.

Key words: transthyretin cardiac amyloidosis, hypertrophy, genetic testing

3. One test, a lifetime of precision familial hypercholesterolemia reports

Authors: **Aditi Babel (1,6))** , Mahmoud Barbir , Emma Neves , Riyaz Patel , Steve E Humphries , Cian Murphy , Theodosia Charitou , Mark Bartlett (1,6)

Affiliations

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[2] Royal Brompton Hospital, London, U.K.
[3] Barts Health NHS Trust, London, U.K.
[4] University College London Hospitals NHS Foundation Trust, London, U.K.
[5] University of Thessaly, Thessaly, Greece
[6] StoreGene Ltd, London, U.K.

Introduction

Familial hypercholesterolemia (FH) affects approximately 1 in 250 people in the UK, of which less than 10% are diagnosed[1]. Here, we evaluate the utility of the StoreGene whole genome sequencing (WGS) approach to comprehensively characterise individuals with FH.

Methods

Saliva samples from 16 participants who met the Simon-Broome FH diagnostic criteria were sent for DNA extraction and sequencing. Four StoreGene reports were generated: 1) FH 4-gene variant assessment, 2) LDL-C polygenic risk score (PRS), 3) *SLCO1B1* variant linked to Simvastatin-induced myopathy, and 4) Lp(a) concentration gene scores. Results were compared to previous biochemical and panel tests by NHS-accredited laboratories.

Results

One sample per participant was used to carry out WGS, and StoreGene reports were generated in 22 days, vs. 2 samples and 42 days for comparator testing[2]. One sample was discarded due to low mapping quality. 15 WGS samples were analysed yielding 100% concordant results with comparators. Identical pathogenic variants were identified in 9 (60%) of cases, with 11 (73%) cases likely to have a polygenic aetiology (LDL-C PRS > 5th decile). The c-index for Lp(a) concentration between the two methods was 0.79. A pharmacogenomic risk variant in *SLCO1B1* was identified in one participant.

Conclusions

StoreGene WGS showed significant benefits where multiple testing is required, including concordant outcomes with available panel tests, faster turnaround time, a wider range of available tests, and minimised sample collection with environmental savings on laboratory consumables. Further research should measure its cost-effectiveness and clinical utility.

[1] Familial Hypercholesterolemia Section (NHS England 2020) (accessed 21/08/2023)
[2] SouthWest Genomic Laboratory Hub Target Turnaround Times (accessed 21/08/2023)

Key words: familial hypercholesterolemia, cardiovascular disease, whole genome sequencing, personalised medicine, pharmacogenomics, diagnostic genomics.

4. Distinct signaling events from the overexpression of the PRKAG2 R302Q variant of AMPK lead to Hypertrophic cardiomyopathy phenotype

Vanya Vaidya[1], Zubin Singh Rana[2], Pradeep Punnakkal[2], Madhu Khullar[3], Ajay Bahl[1]*, Anupam Mittal[4]*

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Introduction: The Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 2 (PRKAG2) cardiac syndrome is characterized by glycogen accumulation in the cardiac tissue that is often associated with unusual patterns of hypertrophy and conduction abnormalities. Variations in PRKAG2 have been associated with rare, early onset autosomal dominant inherited disease that involves ventricular pre-excitation, supraventricular arrythmias and cardiac hypertrophy.
Methods: Using the Trio-exome sequencing, we have analysed a three generation family, which was reported to have a pathogenic variant in PRKAG2 gene that is c.905G>A (p.Arg302Gln) variant. The variant was reconfirmed by Sanger sequencing in the proband and the mother. The proband developed symptoms at the age of 29, while his mother at the age of 60 years. For functional studies, we have made clones for human WT PRKAG2 and the variant (Arg302Gln). To understand the mechanisms involved in disease pathogenesis, H9C2 cardiomyocyte cell line was transfected with mutated and wild PRKAG2 plasmid. We have analysed foetal genes through qRT-PCR, autophagy genes though immunostaining and Western blot and Na^+, K^+ and Ca^{2+} channels through transcriptomics and patch clamp.
Results: PRKAG2 p.Arg302Gln led to hypertrophic phenotype in H9C2 cardiomyocytes. We have observed the increase mRNA expression of foetal genes (ACTA1, MYH6, BETA-MHC, ANP, BNP) which indicates that cells have shifted to hypertrophic phenotype. Confocal microscopy data also corroborated with mRNA expression of foetal genes and the increase in the cell size of the cardiomyocytes was observed. Autophagy marker LC3 expression was found to be decreased as compared to control as was confirmed by confocal microscopy.
Conclusion: Using multi-omics approach, we were able to confirm the progression of hypertrophy due to the variant in the cardiomyocytes.

KEYWORDS: Hypertrophic cardiomyopathy; Glycogen accumulation**;** Conduction abnormalities**;** Autophagy

5. WGS analysis reveals an Alu retrotransposon element insertion in the *NEXN* gene confirming a diagnosis of paediatric onset autosomal recessive dilated cardiomyopathy (AR DCM) in a family

Gable M (1) ; Pennock M ; Nash I ; Williams M ; Whittington R ; Archer B ; Stals K ; Shannon N Berry I .

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We present a paediatric onset AR DCM family where genomic testing was requested in a 4 week old presenting with DCM and strong family history - one sibling died at 7 weeks (SIDS) and second died shortly after birth with DCM. NGS analysis of a bespoke paediatric cardiomyopathy gene panel (2015) revealed a heterozygous *NEXN* nonsense variant, c.424G>T p.(Glu142*), reported as a VUS due to the uncertainty of the inheritance pattern.

With the evolution of genomic testing and increased sensitivity of technologies, trio WGS analysis of the Cardiomyopathies – including childhood onset gene panel (R135) (2022) revealed a heterozygous 299 bp AluYd8 retrotransposon element insertion in the final exon of *NEXN.* Parental testing confirmed the insertion was *in trans* with the nonsense variant; both were subsequently classified as likely pathogenic using ACMG/ACGS variant interpretation guidelines[1,2]. Testing DNA from deceased siblings confirmed the presence of both variants, hence confirming the diagnosis of AR *NEXN*-related DCM.

AR *NEXN*-related DCM is rare with only a small number of cases being reported to HGMD[Pro]. Though AR DCM is a clearly emerging inheritance pattern, as demonstrated by this family, the consequence of heterozygous *NEXN* variants is unclear. The increasing sensitivity of genomic testing improves detection of complex and structural variants in suspected recessive disease, when only one variant has been identified. Trio WGS analysis is a valuable approach in such cases, to determine the inheritance of detected variants.

We present this family and review the AR *NEXN*-related DCM published families to date.

Key words: paediatric onset AR DCM, trio WGS, NEXN gene, Alu retrotransposon.

References: 1) Richards *et al* (2015) Genet Med 17(5):405. ; 2) Ellard *et al* (2020) ACGS guidelines.

6. Understanding the genetic basis of congenital heart disease; whole genome sequencing opens new avenues for investigation, but significant challenges remain.

Verity Hartill[1,2], Mitra Kabir[3], Sunayna Best[2], Kathryn E Hentges[3] and Colin A Johnson[1]

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Acknowledgement: This research was made possible through access to data and findings in the National Genomic Research Library via the Genomics England Research Environment.

Congenital heart disease (CHD) is the commonest congenital defect, affecting around 1 in 100 live births. CHD can be non-syndromic and isolated, or can present as part of a congenital anomaly or neurodevelopmental syndrome. The genetic aetiology of a large proportion of both syndromic and non-syndromic congenital heart disease remains unexplained. A recent focus on "*de novo*" genetic variants has been productive in CHD research, showing that, at least in some cases, heart defects are caused by a new mutation in the affected individual. It is expected that further investigation into the genetic basis of CHD will provide insight into the aetiology of this common congenital anomaly, thus benefitting the wider population.

Here we describe our previous progress using whole exome and whole genome sequencing in families with recurrence of CHD, for example in confirming the links between isolated CHD and motile ciliopathy genes. We discuss our recent study into the genetic causes of CHD within the 100,000 Genomes Project. In this study we have developed a Gene Discovery Pipeline, which combines *de novo* variant analysis with computer-assisted machine-learning, to identify and prioritise candidate genes for CHD (n=79).

Significant challenges remain in CHD genetics, including the confounding effects of genetic heterogeneity, incomplete penetrance, incomplete phenotyping and the complexities of working with large datasets. In spite of these challenges, large scale sequencing projects, such as the 100,000 Genomes Project present many opportunities for advancing our scientific understanding of this common condition.

Key words: Congenital heart disease; genetic heterogeneity; whole genome sequencing;

7. **Prediction of Atrial Fibrillation using Polygenic Risk Scores for Cardiovascular Risk Factors**

Julia Ramírez[1,2], Stefan van Duijvenboden[2,3], William J. Young[2,4], Andrew Tinker[2], Pier D. Lambiase[4,5], Michele Orini[5], Patricia B. Munroe[2]

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Background: Risk stratification for atrial fibrillation (AF) is suboptimal despite high cardiovascular comorbidity and mortality. Polygenic risk scores (PRSs) for AF predict risk independently from traditional risk factors. We assessed utility for risk stratification when including PRSs for multiple cardiovascular traits.

Methods: 379,574 European participants from UK Biobank without known cardiovascular conditions were included (median follow-up 11.5 years, 6.4% AF cases). In a training subset (50%), we built three scores using AF risk factors in Cox analyses. Score s1 included sex and age, score s2 included s1 and an AF PRS, and s3 included s2 and multiple PRSs for cardiovascular traits that remained independently associated with AF. In an independent test subset (50%), we evaluated performance using the area under the curve (AUC), hazard ratios (HRs) and net reclassification index (NRI).

Results: PRSs for coronary disease, body mass index, systolic blood pressure, triglycerides, PR interval, QRS duration and heart rate were included in s3. Score s3 had a higher AUC than s2 (0.749 versus 0.747, P=1.6x10^{-9}). The HR (95% confidence interval) for individuals in the top versus bottom 20% of the s3 distribution was 4.81 (4.62–5.00), versus 4.76 (4.57– 4.95) for s2. Mean NRI for s3 versus s2 was 1.8%. Score s3 reclassifies 1,757 individuals as ≥10% AF risk, where 168 would have an AF event within the follow-up period.

Conclusions: Although our results require validation, they suggest adding PRSs for multiple cardiovascular traits improves risk stratification for AF, potentially identifying individuals who may benefit from early prevention measures.

Key words: Atrial fibrillation; complex genomics; cardiovascular risk; polygenic risk scores

8. Risk stratification for advanced atrioventricular block using electrocardiogram trait polygenic risk scores.

William J. Young[1,2], Julia Ramírez[1,3], Helen R. Warren[1], Stefan van Duijvenboden[1,4], Andrew Tinker[1], Pier D. Lambiase[1,5], Patricia B. Munroe[1]

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Background: Every year, >1 million pacemakers are implanted worldwide for advanced (2nd/3rd degree) atrioventricular block (AV-block), a potentially life-threatening cardiac rhythm disturbance. Electrocardiogram trait polygenic risk scores (PRS) are associated with AV-block independent of age and sex. However, to determine clinical utility, we must assess their performance alongside other risk predictors.
Methods: PRSs for PR-interval, spatial QRS-T angle (spQRSTa), P-wave and QRS-duration were constructed in European ancestry participants from UK-Biobank using previously reported

lead genome-wide significant variants. 10-year AV-block risk (5,991 cases; 351,460 controls) was evaluated in Cox regression models adjusted for covariates age, sex, systolic blood pressure, prevalent diabetes, coronary disease and heart failure. Hazard ratios were calculated for all individuals, and after stratifying for sex and age. A Bonferroni-corrected significance threshold was applied (P<0.0125). Area under the curve (AUC) was calculated to compare performance when adding a PRS to the clinical predictors alone.
Results: Each PRS was independently associated with incident AV-block (hazard ratios [HR] range between 1.05-1.24). Comparing top vs bottom PRS deciles, HRs were: PR-interval 2.18 (1.86-2.56); P-wave 1.26 (1.08-1.47); spQRSTa 1.25 (1.07-1.45); QRS-duration 1.19 (1.03-1.39). Significant stratified analyses results were: QRS-duration and spQRSTa PRS for individuals <60 years; P-wave duration if >60 years; P-wave and spQRSTa PRS for males. The PR-interval PRS was significant in all analyses. AUCs did not significantly differ vs covariates alone.
Conclusions: Our findings highlight age and sex-specific associations for AV-block risk using electrocardiogram PRS. Larger case sample sizes in younger cohorts may identify applications for risk stratification earlier in life.

Key words: Polygenic risk scores, conduction disease, atrioventricular block, risk stratification

9. 'Genetic analysis of Omani families with cardiomyopathies and arrhythmias'

Fahad Al Hattali[1,2,3], Pier Lambiase[2], Andrew Tinker[3]

1. *National Genetic Centre, Royal Hospital, Muscat, Oman*
2. *Institute of Cardiovascular Science, University College London, London, UK*
3. *William Harvey Research Institute, Queen Mary University of London, London, UK*

ABSTRACT

Whole Exome Sequencing (WES) on trios i.e., patient and parents has proven an efficient way to identify variants in many families and thus in this study we preformed trio-WES on five Omani families with cardiomyopathies and arrhythmias. The index patients were already subjected to an almost comprehensive panel of genes related to cardiovascular diseases.

Nonacus Cell3 exome library preparation kit was used for the trio WES. Prioritization for rare and exonic variants were done using Exomiser and Qiagen softwares based on the hypothesis that the mode of inheritance is Autosomal Recessive (AR) since all families are of consanguineous marriages. Then final variants were confirmed using Sanger sequencing and segregated to the affected/ unaffected family members. The next step involved generating induced Pluripotent Stem cells (iPSc) and then differentiated them into cardiomyocytes and then we knockdown the genes of interest using siRNA and measure the effect using qPCR and Calcium Transient Assay.

One family showed a variant in the ALPK3 gene which already associated with HCM and DCM. Three families analysis showed three variants shared following AR inheritance which have never been associated with cardiovascular phenotype. One family showed no shared variants. Based on prediction of pathogenicity we selected, RAD9A, AFF4 and HMGA1 genes for siRNA knockdown using in vitro iPSc-CMs. Quantitative PCR (qPCR) showed that we successfully suppressed more that 80% of the genes at 80nM siRNA. The Calcium Transient imaging assays using Flu-4 is yet to be completed which will compare rise time, calcium transient duration at 50% and 90% of decay following the peak amplitude and change in amplitude.

Trio-WES revealed shared variants following AR inheritance that never been associated with cardiovascular phenotype. Functional characterization using iPSC-CMs followed by siRNA knockdown of novel genes is a great way to established new causative genes in cardiovascular diseases.

KEYWORDS ; Whole exome sequencing (WES); Trio-WES; siRNA, cardiovascular risk, arrhythmia, cardiomyopathy

10. **CARDIAC GENETICS REFERRALS: SRI LANKA'S SINGLE CENTRE EXPERIENCE OVER 7 YEARS**

Vindya Subasinghe*; Vajira Dissanayke*

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INTRODUCTION

Genetics is an evolving field in Sri Lanka. Genetic testing facilities have gradually developed, but it is not yet available for free of charge for patients in the government sector, despite free health in the island. Cost of testing is the main obstacle for more testing opportunities. Significant proportion of referrals for whole exome sequencing are directed to a university centred laboratory located in the financial capital of Sri Lanka.

METHODS

Patients who were referred with cardiac phenotype and those who have been identified with variants in genes related to cardiac phenotype were filtered using the local Clinical Genetics Database for whole exome sequencing. Demographic data, phenotypic and genotypic data were analysed using electronic proforma.

RESULTS

Total of 13 referrals were included: 46 % of the referrals received in the last 2 years. Cohort comprises 61 % females. The Ages range from 8 months to 32 years. Number referred with primary cardiac phenotype was 10: no variant identified in 1 (10%) . Out of those where variant was identified, 66.6 % were cardiomyopathies (50 %; likely pathogenic, 50 %; variant

of uncertain significance [VUS]), 1(11.11%) each with valvular pathology, and arrhythmogenicity. Detection of paternally inherited 2 VUS in cardiomyopathy related genes among one patient (11.11%) with cardiomyopathy and dysmorphism. Incidental detection of variants in cardiac genes were seen in 3 patients over the study period.

CONCLUSION
Recent increasing trend in receiving referrals noted. Variant detection rate is satisfactory. Non availability of a wide range of testing for example microarray creates the gap in evaluating individuals with inherited variants of uncertain significance which are phenotypically not fully correlated.
Key words: Cardiac genetics; Genetic referrals; Sri Lanka

11. **Two further paediatric cases of *ADAR* interferonopathy with valvular calcification as the most prominent feature**

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Cardiac valvular calcification is highly prevalent in the elderly; however, it is extremely rare in childhood, and reported in association with rheumatic heart disease, and some genetic disorders, including: Hutchinson-Gilford progeria and Singleton-Merten syndromes; Gaucher disease; and disorders of altered extracellular purine/inorganic pyrophosphate (PPi)/inorganic phosphate (Pi)..

Recently, severe and progressive cardiac valvular calcification was described in four children, on the background of a primarily neurological phenotype involving ataxia, who all had biallelic pathogenic *ADAR* variants. This promoted the recommendation for periodic cardiac screening in patients with this interferonopathy.

We report two further cases with paediatric onset significant valvular calcification.

The first patient, now 17 years of age, presented three years earlier with breathlessness on exertion. Aortic and mitral valvular calcification was diagnosed, necessitating valve replacements. Additional phenotypic features include relative short stature, clawing of toes and freckles. Trio exome sequencing revealed the biallelic *ADAR* pathogenic variants. Peripheral contractures have progressed, with normal nerve conduction studies and normal brain imaging.

The second patient, now 30 years of age, was investigated for ataxia at the age of two years. She has a mild movement disorder but the major problem has been recurrent calcification of her mitral and aortic valves, requiring aortic replacement at 12 and mitral replacement at 17 years; followed by repeat valve replacements aged 30, for recurrent valve calcification. Exome sequencing revealed biallelic ADAR mutations.

These two further cases demonstrate that calcific valvular disease is part of *ADAR* interferonopathy and could be the most prominent or heralding feature.