THE GENOMIC MEDICINE FOUNDATION (UK)

FELLOWSHIP, SCHOLARSHIP, EDUCATION AND PROMOTION OF GENOMIC APPLICATIONS IN MEDICINE, HEALTHCARE AND SOCIO-ECONOMIC PROGRESS

THE 7TH INTERNATIONAL CARDIOVASCULAR GENOMIC & MEDICINE CONFERENCE

4 & 5 DECEMBER 2019
PARK INN, YORK

DIRECTORY

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

30th November 2019

To All Faculty, Speakers and Delegates

Welcome to the VII International Cardiovascular Genomic Medicine Conference incorporating the original Cardiff Cardiovascular Genetics Conference.

Since 2007, the Biennial International Cardiovascular Genetics Conference has established its place as a credible platform and opportunity for sharing recent advances and new knowledge related to genetic and genomic aspects of cardiovascular sciences. From start, the emphasis has been on translation and applications in clinical cardiovascular medicine and surgery. The last convention was held in Cardiff in October 2017.

The VII ICVGM is held with the theme of **'Clinical Cardiology in the Genome Era'.** This objective is most pertinent in keeping with the fast moving transformation of clinical medicine within the realms of *Genomic and Precision Medicine.* The future practice of Cardiovascular Medicine and Surgery now included targeted *next generation genome sequencing* in making precise diagnosis, multidisciplinary care, assessing the prognosis, genetic counseling of close family members with the option of targeted cascade genomic testing, long term clinical surveillance and prevention of serious life threatening complications with the help of drug and electrophysiological interventions. Recent advances in identification of new genes, delineation of rare inherited cardiovascular diseases, understanding the molecular mechanisms has helped in discovering and development of new drugs.

On behalf of the Organizing and Scientific Program committees, I am truly grateful to all of you for delivering the superb program and participating in this major convention. Contents and quality of many presentations focus on the cutting edge genome science and clinical cardiology practice.

Without your support and invaluable input this conference would not have been successful. We are grateful for generous support of the British Heart Foundation and many other sponsors who made this conference possible and viable. The Federation of the UK Royal Colleges of Physicians has approved this conference for 12 hours of continuous professional credits, a reflection and acknowledgement of the aims and objectives of cardiovascular genomic medicine.

With best wishes and grateful thanks

Professor Dhavendra Kumar

Chair- Organizing and Scientific Committees VII ICVGM 2019 & Medical Director/CEO-The Genomic Medicine Foundation (UK)

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

VII INTERNATIONAL CARDIOVASCULAR GENOMIC MEDICINE CONFERENCE

"CLINICAL CARDIOLOGY IN THE GENOME ERA"

4-5 DECEMBER 2019, YORK, ENGLAND, UK

To All Faculty, Speakers and Delegates,

As the new Patron of the Genomic Medicine Foundation, it gives me great pleasure to welcome you to the VIIth International Cardiovascular Genomic Medicine Conference.

I was proud and honoured to be asked to become the Patron of the Foundation after the sad death of Sir David Weatherall, the inaugural Patron, and one of the Giants of Medicine. I hold the David Weatherall Chair of Medicine at the University of Liverpool, and met David many times to discuss genomics and its role in Medicine. Cardiovascular Medicine is certainly one of the growth areas for genomics and I am sure that the use of genomic technologies will become part of routine clinical practice in the coming years.

The Genomic Medicine Foundation serves an important role in enhancing the knowledge base and disseminating evidence about genomic medicine in healthcare. Its objective to improve global health and enhance socio-economic progress in developed and developing nations is laudable and I am sure supported by all of us. In my work, I am particularly keen to ensure that genomic and precision medicine does not just become the province of the richer nations, but is also embraced by the developing world. Indeed, even within the UK, it is important that the benefits of genomics help the whole population irrespective of their wealth, ethnic background, social class or geography.
There are of course already many health inequalities within the UK, and I was particularly pleased to see that the NHS long term plan has made tackling health inequalities a major objective, in addition to progressing personalised medicine within the NHS, following on from the success of the 100,000 genomes project.

Dhavendra Kumar and the scientific committee have developed an excellent program for this conference which will focus on cutting-edge advances in cardiovascular medicine. The conference succeeds the previous highly successful meetings which were held in Cardiff. I hope you enjoy the conference and continue to support this important and advancing area of Medicine.

Professor Sir Munir Pirmohamed, MB ChB (Hons), PhD, FRCP, FRCP(E), FFPM, FRSB, FBPhS, FMedSci

David Weatherall Chair of Medicine and NHS Chair of Pharmacogenetics
Director, MRC Centre for Drug Safety Science and Wolfson Centre for Personalised Medicine
Institute of Translational Medicine
University of Liverpool
1-5 Brownlow Street
Liverpool, L69 3GL, UK

UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE | MRC Centre for Drug Safety Science

VII INTERNATIONAL CARDIOVASCULAR GENOMIC MEDICINE CONFERENCE

"CLINICAL CARDIOLOGY IN THE GENOME ERA"

4-5 DECEMBER 2019, YORK, ENGLAND, UK

ACKNOWLEDGEMENTS

The organizing committee of the VII International Cardiovascular Genomic Medicine Conference gratefully acknowledges support and collaboration of all faculty, speakers, poster presenters, delegates, volunteers and sponsors for making this convention successful. In addition, a number of colleagues and invisible sources offered guidance and encouragement in the planning and organization of this event.

Finally, this convention would not have been possible without the painstaking efforts of the Neon Events Management and the Conference Unit at the Park Inn by Radisson Hotel in York. Our special thanks and appreciation to all staff associated with these corporations.

Professor Dhavendra Kumar
Chair- Organizing Committee
VII ICVGM 2019, York, England, UK

SCIENTIFIC COMMITEE

Professor Dhavendra Kumar
Genomic Medicine Foundation & William Harvey Research Institute, Queen Mary University of London

Professor Perry Elliot
University College London & Inherited Heart Diseases Unit, Bart's Hospital, London, UK

Professor Bill Newman
Centre for Genomic Medicine, University of Manchester, UK

Professor Elijah Behr
St George's, University Of London, UK

Professor Arthur Wilde
University of Amsterdam
The Netherlands

Professor Bart Loeys
University of Antwerp
Belgium

Professor Robert Hamilton
Hospital for Sick Kids, University of Toronto
Canada

Professor Ajay Bahl
Department of Cardiology
PGIMER, Chandigarh, India

Dr. Lorenzo Monserat
Health-n-Code
La Coruna, Spain

Professor Ingrid Winship, University of

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

"The 7th International Cardiovascular Genomic Medicine Conference"

'Clinical Cardiology in the Genome Era- From Genome Diagnosis to Therapy of Inherited Cardiovascular Diseases'

4-5 December 2019

Park Inn by Radisson Hotel, York, England, UK

Approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 12 category 1 (external) CPD credit(s) (code 125402)

Scientific Programme

Scientific Committee

Dhavendra Kumar (Cardiff, UK)- Chair
Perry Elliott (London, UK)
Bill Newman (Manchester, UK)
Elijah Behr (London, UK)
Arthur Wilde (Amsterdam, NL)
Bart Loeys (Antwerp, Belgium)
Robert Hamilton (Toronto, Canada)
Ajay Bahl (Chandigarh, India)
Lorenzo Monserrat (La Coruna, Spain)
Ingrid Winship (Melbourne, Australia)

Day 1:

0800 **Registration**

0900 **Welcome/ Introduction** **Dhavendra Kumar**

0905 **Session 1:** **'Phenotype-genotype ontology of inherited cardiovascular conditions'**
Chair: Professor Ruth New-Bury Ecob, Bristol, UK

0905 **Congenital heart disease**
Catherine Mercer, Clinical Genetics Unit, University of Southampton, UK

Genotype-phenotype correlations in familial dilated cardiomyopathy

0920 *Diana Fatkin, Affiliation: Victor Chang Cardiac Research Institute, Sydney, NSW, Australia*

0940 **Aortic & arterial phenotypes**
Bart Loeys, University of Antwerp, Belgium

1000 **Primary lymphatic anomalies- an update**
Sahar Mansour, St. George's Hospital, London, UK

1015 **Role of Myocardin in smooth and cardiac muscle development** *A. Houweling, Molecular Cardiology Unit, Academic Medical Center, Amsterdam, The Netherlands*

1030 **Plenary 1:**
'Genomics led personalised prescribing in cardiovascular medicine'
Professor Sir Munir Primohamed, Liverpool, UK

Chair: Professor Patricia Munroe, QMUL, London, UK

1145 **Tea/Coffee/Exhibitors**

1115 **Session 2: 'Novel genes and molecules underpinning cardiomyopathies'**
Chair: Professor Perry Elliott, UCL/Bart's, London, UK

1145
Sarcomere- novel genes and related molecules
Lorenzo Monserrat, Cardiovascular Genomics Laboratory (HealthinCode), La Coruna, Spain

1205
MYH7 variant in Egyptian HCM patients
Mona Allouba, Aswan Heart Centre, Egypt

1220
Titin and related genes/molecules
James Ware, Imperial, University of London, UK

1240
A fresh look at dystrophin in cardiomyopathy'
Federica Montanaro, UCL Great Ormond Street Institute of Child Health

1300

LUNCH

1415

Session 3: 'Heterogeneity of disorders of cardiac conduction & rhythm'
Chair: Dr. John Dean, Aberdeen, Scotland, UK

1415 **Brugada syndrome- Mendelian, Oligogenic or Multigenic?**
Elijah Behr, Cardiovascular Medicine, St. George's, London, UK

1435 **Genomic complexity of atrial fibrillation**
Rui Providencia and Pier Lambiase, Cardiovascular Research Centre, University College of London, UK

1455 **Whole genome and transcriptome sequencing of post-mortem cardiac tissues from sudden cardiac death victims**
S.B. Jacobsen, Section of Forensic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

1505 **The Egyptian Collaborative Cardiac Genomics (ECCO-GEN): Defining a Healthy Volunteer Cohort**
Yasmine Aguib, Aswan Heart Centre, Egypt

1520 TEA/ COFFEE/ POSTERS

1545 Plenary 2- Keynote Lecture: "The Sir William Harvey Oration"

Life long pursuit of Inherited Cardiovascular Conditions
Professor Bill McKenna, Cardiovascular Medicine, University College London, London, UK

Introduction/ Citation by Professor Dhavendra Kumar

1645 Session 4: Clinical Cardiovascular Genomic Medicine

Chair: Professor Ajay Bahl, Chandigarh, India

1645 **The Miles Frost Hypertrophic Cardiomyopathy Prevention- a model for Preventive (Community/Public Health) Cardiology**
Morven Dunn & Joanne Whitmore, The British Heart Foundation, London, UK

1700 **Outcomes of the next generation genome diagnosis for inherited cardiac conditions**
Tessa Homfray, Clinical Genetics Unit, St.George's Hospital, London, UK

1715 **Hypertrophic Cardiomyopathy & Pregnancy Outcomes in North India**
Pooja Sikka, Department of Obstetrics & Gynecology, Post Graduate Institute of Medical Education & Research, Chandigarh, India.

1730 **Multi-Disciplinary team for delivering the NHS cardiovascular genomic medicine service**
Gerry Carr-White, St. Thomas/ Guy's Hospitals, London, UK

Reflections & Discussion on Day 1

1745 **CLOSE**

1800 **Welcome Drinks Reception**

1900 **GALA DINNER**

Day 2: 5th December 2019

0800-0830 **Registration**

0830 **Session 5:** **'Genomic research applications in complex cardiovascular conditions'**
Chair: Dr. Maite Tome, St. George's, London, UK

0830 **Polygenic score and complex cardiac conditions**
Emanuale Di Angelantonio, University of Cambridge, UK

0850 **Stroke genetics & genomics in clinical arena**
Hugh Markus, Adenbrooke's Hospital, University of Cambridge, UK

0910 **Systemic Hypertension- outcomes of genomic studies**
Patricia Munroe, The William Harvey Heart Centre, QMUL, London, UK

0930 **Genomic insights in aortic & arterial diseases**
Julie de Backer, University of Ghent Hospital, Belgium

1000 **Plenary 3:** **'The Genomic Revolution in Pediatric Clinical Cardiology'**
Prof. Seema Mittal, Sick Kids Hospital, Toronto, Ontario, Canada.
Chair: Dr. Juan Kaski, GOSH, London, UK

1100 **Tea/Coffee/ Posters**

1130 **Session 6: 'Cardiovascular Genomic Medicine Research'**
Chair: Professor Elijah Behr, London, UK

1130 **Defining cardiovascular diseases at scale using multimodal electronic health records**
Tom Lumbers, University College London, UK

1150 **Pertinent Issues in cardiovascular diagnostic genomic testing**
Ellen Thomas, Genomics England, QMUL/Imperial, London, UK

1210 **Challenge of variant classification in cardiovascular medicine: The example of hypertrophic cardiomyopathy**
S. Fokstuen, Service of Genetic Medicine, University Hospitals of Geneva, Geneva, Switzerland

1230 **Development of the Indian Inherited Cardiovascular Conditions Database**
Ajay Bahl, Post Graduate Institute of Medical Education & Research, Chandigarh, India

1250- 1430 Poster viewing & Lunch

Session 7: 'Novel genomic/molecular cardiovascular therapeutics approaches'
Chair: Professor Dhavendra Kumar, QMUL, London, UK

1430 **Novel therapeutic advances in arrhythmogenic cardiomyopathy**
Angeliki Asimaki, Cardiovascular Medicine, St. George's, London, UK

1450 **Stem cell and related therapeutic advances in hypertrophic cardiomyopathy**
Matthew Daniels, Department of Cardiology, University of Oxford & University of Manchester, UK

COFFEE/TEA

1515

Session 8: Open Presentations (selected from submitted abstracts)

1530

- **Prize for best presentation**
- **Panel of 3 judges Dr. Sarju Mehta, Cambridge, UK**
  Ms. Melanie Watson, Southampton, UK
  Dr. Sam Mohaddin, Bart's, London, UK

Note: 7 minutes including 2 minutes discussion

1530 Heart failure, severe arrhythmia and sudden cardiac death in Marfan syndrome and related heritable thoracic aortic diseases
Anthony Demolder, Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

1540 Atypical *COL3A1* variants (glutamic acid to lysine) cause vascular Ehlers-Danlos Syndrome with a consistent phenotype of tissue fragility and skin hyperextensibility
Neeti Ghali, Ehlers-Danlos Syndrome National Diagnostic Service London, North West Thames Regional Genetics Service, London North West Healthcare University NHS Trust, Harrow, Middlesex, UK

1550 **Genome sequencing for inherited cardiac conditions: analysis of 201 cardiovascular patients recruited through the 100,000 Genomes project by the West of England and South West NHS Genomic Medicine Centres.**
Rebecca Whittington, Clinical Genetics, Bristol University Hospitals NHS Trust, Bristol, UK

1600 **Major Genetic Contributors to Non-syndromic Tetralogy of Fallot**
Richard Monaghan, Cardiovascular Medicine, University of Manchester, UK

1610 **Identifying Long QT syndrome patients in primary care: A population- based case control study**
WRH Evans, PRISM group, Division of Primary care, University of Nottingham, UK

1620 **Biallelic *PPP1R13L*-associated paediatric dilated cardiomyopathy: expanding the phenotypic spectrum**
Claire Turner, Department of Clinical Genetics, Royal Devon & Exeter Hospital, Exeter, UK

1630 **Panel comments, summing up and the best presentation award**

1635 **Plenary 4: 'Dilated Cardiomyopathies- new paradigms for cardiovascular genomic medicine'**
Professor Perry Elliott, Director- Cardiovascular Research Institute, University College London and Lead Consultant Cardiologist of the Inherited Heart Diseases Unit, St. Bart's Hospital, London, UK
Chair: Professor Nigel Wheeldon, Sheffield, UK

1715 **Questions/ Reflections**

1730 **Prizes/ Vote of Thanks/ Close**

Good Bye/ Bon voyage

Key Note Lectures

Plenary 1.

Professor Sir Munir Pirmohamed, MB ChB (Hons), PhD, FRCP, FRCP(E), FFPM, FRSB, FBPhS, FMedSci

David Weatherall Chair of Medicine and NHS Chair of Pharmacogenetics
Director, MRC Centre for Drug Safety Science and Wolfson Centre for Personalised Medicine
Institute of Translational
Medicine University of Liverpool,
Liverpool, UK

'Genomics led personalized prescribing in cardiovascular medicine'

Cardiovascular disease (CVD) remains an important cause of morbidity and mortality worldwide despite the recent successes in drug therapy and cardiac interventions which have led to improved patient outcomes. Response to drugs in CVD is often variable, with some patients responding well, others not responding at all, while a small proportion may get adverse effects. The ability to identify non-responders and adverse responders, and providing with alternative therapeutic options, may help further in improving clinical outcomes. This will be further discussed in the lecture by focusing on three therapeutic areas and their individual genetic determinants: anticoagulants, anti-platelet agents and statins. Another area to consider for the future is the utility of polygenic risk scores, and whether they will help in identifying responders to certain drugs. Further work is needed in this area. There is also a drive in cardiovascular medicine towards to the use of the polypill, providing avenues for population level prevention. However, we should not consider this to be a competition between the two approaches (precision medicine vs polypill), and they are in fact complementary, and the future approaches may include the use of "personalised" polypills.

Plenary 2

The Sir William Harvey Oration

William J. McKenna, MD

William McKenna is Canadian (BA - Yale, MD - McGill). He is CEO & Medical Director, Heart Hospital, Hamad Medical Corporation in Qatar. He is also Associate Dean for Research (Weill Cornell Medicine - Qatar) and Emeritus Professor of Cardiology (UCL). Previously he established the Inherited Cardiac Disease clinic at St George's Hospital and then at the Heart Hospital – University College London. His main interests have been in clinical and basic research of the cardiomyopathies. His recent work has contributed to the identification of disease-causing genes in HCM, DCM and ARVC, to the establishment of new diagnostic criteria within the context of familial disease, and to the establishment of algorithms to identify patients at high risk of sudden death.

Abstract

"Lifelong pursuit of inherited cardiovascular disease: focus on the cardiomyopathies"

Recognition of disease phenotypes and the familial and genetic basis of the cardiomyopathies took place during the latter decades of the last century. Recent advances focus on elucidation of disease mechanisms as potential targets for treatment. Initially, the diagnosis of cardiomyopathies was made by recognition of disease features in the absence of other causes, i.e. a diagnosis of exclusion. Until recently the diagnosis of dilated cardiomyopathy (DCM) has incorporated patients with an initial clinical presentation of heart failure and/or arrhythmia. Recent recognition of genetic causes of a predominantly arrhythmic cardiomyopathy (ACM), which may have overlapping structural and functional features with DCM, has led to the distinction between DCM, a condition characterized by cardiac failure, and ACM, characterized by arrhythmia. The recent designation of ACM to include genetic (e.g. desmosomal, lamin, FLNC, desmin mutations), as well as acquired causes of a cardiomyopathy (sarcoidosis, Chagas, myocarditis) with a predominantly arrhythmic presentation, will help to better characterize patients in relation to diagnosis and outcomes. Despite the fact that the genetic basis of the cardiomyopathies has been known for between 20 and 30 years, progress has been slow in developing targeted therapies but some are now evolving.

Keywords: Hypertrophic cardiomyopathy; Dilated Cardiomyopathy; Arrhythmogenic cardiomyopathy; Genetics; Sudden death

Plenary 3

Dr. Seema Mital is a Heart Failure and Transplant Cardiologist and Head of Cardiovascular Research at the Hospital for Sick Children, Toronto. She is Professor of Paediatrics at the University of Toronto and a Senior Scientist at the SickKids Research Institute. She is also the Heart and Stroke Foundation of Ontario Chair of Cardiovascular Science, and the Scientific Co- Lead of the Ted Rogers Centre for Heart Research.
Seema Mital has a strong translational research program focused on genomics, pharmacogenomics and stem cell applications to model childhood heart disease and discover new therapies. She has extensive experience in the genetics/genomics of congenital heart disease and heart failure, personalized medicine and clinical trials. She established the SickKids Heart Centre Biobank, a multi-centre biorepository of children and adults with childhood onset heart disease for genomics research, one of the largest international repositories of its kind.

Sheis the Scientific Co-lead of the Ted Rogers Centre for Heart Research Cardiac Precision Medicine Program established in November 2014.
Mital is a Principal Investigator of the CIHR-funded Canadian National Transplant Research Program, the NIH-funded Pediatric Heart Network, and leads the ERAPerMed funded PROCEED network for Personalized Genomics in congenital heart disease. She serves on the Leadership Committee of the Functional Genomics and Translational Biology Council of the American Heart Association, and the Heart and Stroke Foundation Structural Heart Disease Council.

The Genomic Revolution in Clinical Cardiology

Genomics is at the forefront of major discoveries that have the potential to change the way we practice medicine. The practice of genomics is at the heart of precision medicine approaches to disease prevention, diagnostics and therapeutics. This talk will focus on precision medicine from the lens of childhood heart disease. Whole genome sequencing is allowing us to look beyond coding regions of the genome to find the hidden causes of cardiomyopathies and congenital heart disease. Machine learning approaches are facilitating integration of clinical and genomic data into risk prediction models for outcomes in heart disease. And genomic discoveries are driving the development of targeted therapeutics as well as the search for genetic cures.

Plenary 4

Perry Elliott, MD FRCP

Prof. Perry M. Elliott (H-index 98) is Professor of Cardiovascular Medicine at University College London (UCL) and a Senior Investigator of the UK National Institute for Health Research (NIHR). He is director of the UCL Centre for Heart Muscle Disease, Head of Clinical Research at the Institute of Cardiovascular Science UCL and a consultant cardiologist in the Centre for Inherited Cardiovascular Disease at the Bart's Heart Centre, St. Bartholomew's Hospital London, UK. He is Chairman of the ESC Heart Academy and Chairs the ESC Council on Cardiovascular Genomic. He is past Chairman of the ESC Working Group on Myocardial and Pericardial Diseases (2010–2012) and the Executive Committee for the European Outcomes Research Programme registry on cardiomyopathies, chair of the ESC Guideline Task Force on Hypertrophic Cardiomyopathy, member of the Congress Programme Committee 2018-2020 and a member of the ESC Managerial Council 2018-2020. He is President of Cardiomyopathy UK, Europe's foremost charity for patients with heart muscle disease. From 2009 to 2013, he was Deputy Editor of *The Heart Journal* and is currently Deputy Editor for the International Journal of Cardiology.

Over the past 25 years, Prof. Elliott has established an international reputation in the field of heart muscle disease, authoring more than 400 peer-reviewed papers on the subject.
He develops diagnostic standards, risk stratification tools and clinical service models based on some of Europe's largest inherited heart disease cohorts, fostering industry collaborations in sequence interpretation, therapeutic trials and multicentre research partnerships.

'Dilated Cardiomyopathies- new paradigms for cardiovascular genomic medicine'

Professor Ajay Bahl
Department of Cardiology
PGIMER, Chandigarh, India

Development of the Indian Inherited Cardiovascular Conditions Database

Despite a large population, there is scant genotyping data on the Indian cardiomyopathy patients. This is because the priority area is coronary artery disease. In addition, genotyping usually doesn't directly affect management, is expensive and had limited support from research agencies. Clinical data on mutations in Indians is needed since upto 50% mutations were found to be novel. In 2016, 2017 and 2018, there were only 1, 2 and 4 published studies respectively on genotyping cardiomyopathies from India. This scarcity of data should be offset by a high quality database that can be gradually built up. This can be supplemented by data from the Indian expatriate population. The Indian cardiomyopathy database aims to provide a detailed clinical and family profile, outcomes, serial ECGs, serial representative echocardiographic images and other investigations whenever feasible. With wider availability of genotyping services, clinicians are going to frequently encounter patients in whom sequence variations/ mutations have been identified. A strong database can go a long way in helping clinicians make sense of these sequence variations. A lesson learned from this database is that mutations that cause restrictive physiology are often reproducible in different populations and carry a worse prognosis.

Key words: Cardiomyopathies; database; mutations; Indians.

Angeliki Asimaki

Prior to joining St. George's in 2017, Dr. Asimaki was a research associate at the Beth Israel Deaconess Medical Centre (BIDMC) and an instructor in Cardiovascular Pathology at Harvard Medical School (HMS) in Boston, USA. She has been recognized with several highly competitive young investigator awards and is an author on >50 peer-reviewed research papers and >10 invited submissions. She has published major first-author papers in the New England Journal of Medicine and Science Translational Medicine and she has been invited to give lectures in >50 international conferences as well as several seminar talks both in the US and Europe.

Arrhythmogenic cardiomyopathy (ACM) is characterized by redistribution of junctional proteins, arrhythmias, sudden death and progressive myocardial injury. Despite progress in identifying genetic determinants of the disease, the exact mechanisms of pathogenesis remain unknown. We performed a high-throughput screen in a zebrafish model of ACM and showed that one compound, SB216763 (SB2), could mitigate the disease not only in the fish but also in two different mouse models of ACM. SB2 has been annotated as a specific inhibitor of the enzyme GSK3β. Further studies proved that the enzyme has a key role in the pathogenesis of the disease. However, chronic inhibition of GSK3β in patients would come with risks. Accordingly, we looked downstream of this enzyme in search of further central pathways of disease. Inflammation is a prominent feature of ACM but whether it contributes to the disease phenotype or is a consequence of myocardial injury is unknown. We showed that inflammatory signalling is activated in ACM and in fact drives key features of the disease. An inhibitor of NF-κB, a master regulator of inflammation, could alleviate the disease in three different experimental models. These studies suggest that targeting inflammatory pathways may be an effective new mechanism-based therapy for ACM.

Dr. Catherine Mercer, MD FRCP

Dr Catherine Mercer is a Consultant Clinical Geneticist at University Hospital Southampton NHS Foundation Trust and an Honorary Senior Lecturer at the University of Southampton. She works as the Wessex Cardiac Genetics Lead, and along with the team, covers a population of 3.5 million. Dr Mercer has expertise in caring for families with isolated familial cardiac disease as well as those with syndromic diagnoses that include a cardiovascular component. Dr Mercer is active in research regarding gene identification, including the discovery of both *NR2F2* in patients with left ventricular outflow tract obstruction and more recently a novel monogenic cause of familial Ebstein's anomaly.

Abstract:

'Genomic profiling in monogenic malformation syndromes with cardiovascular phenotype'

Approximately 30% of congenital heart disease is thought to be related to genetic syndromes accompanied by extra-cardiac anomalies. Understanding genetic aetiology in those with both a cardiovascular phenotype and other anomalies can help clinicians to effectively plan a patient's surgical and medical management and their follow-up.

Over recent years, molecular diagnostic testing in patients with syndromic diagnoses has become increasingly sophisticated. Prior to this, genetic testing was carried out on, at most, one or a few loci. The advent of array comparative genomic hybridisation changed this landscape by allowing a patient's entire genome to be interrogated at improved resolution, thereby allowing the detection of medium to large genomic variation. Today, this can be done at single-nucleotide resolution as a result of cheaper, faster and increasingly accurate whole-exome sequencing and whole-genome sequencing.

Using the case example of gene discovery in a family with X-linked Ebstein's anomaly with an associated skeletal phenotype affecting 6 individuals over 2 generations, the power of next generation sequencing will be illustrated in gene discovery. An overview will also be given of genomic testing methods routinely used in clinical practice including their effectiveness and limitations.

Diane Fatkin, University of Melbourne, Australia

Genotype-phenotype correlations in familial dilated cardiomyopathy

Familial dilated cardiomyopathy (DCM) is generally considered to be a monogenic disorder that results from single rare genetic variants that are sufficient alone to cause disease. This disorder is genetically heterogenous with more than 100 putative disease genes identified to date. Variants in these genes can be associated with diverse clinical manifestations. The assumption underlying genotype-phenotype correlations is that the genotype is the main determinant of the cardiac phenotype. Precision medicine approaches to patient care necessitate consideration of each individual's unique suites of genetic and environmental risk factors, prompting the need to understand how these factors might interact with primary gene mutations to modify disease features. Truncating mutations in the *TTN* gene (*TTN*tv) are the most common genetic cause of familial DCM. The age of onset and disease severity in symptomatic *TTN*tv carriers varies widely. Moreover, *TTN*tv are present in up to 3% of the general population. These observations suggest that additional modifying factors might be "in the mix". To study the effects of *TTN*tv and "second hit" factors on cardiac function, we are using a novel zebrafish model of a human A-band *TTN*tv. Identification of clinically-relevant disease-modifying factors is important for family management and may enable DCM onset to be delayed or prevented.

Key words: dilated cardiomyopathy, genetics, environment

Professor Elijah Behr, MD FRCP
Department of Cardiovascular Medicine
St. George's Hospital Medical School
University of London, UK

"**Brugada syndrome- Mendelian, Oligogenic or Multigenic?"**

Dr. Ellen Thomas is Clinical Lead for NHS Genomic Medicine at Genomics England, as well as a Locum Consultant in Genomic Medicine at Imperial College NHS Trust. Her training included a PhD thesis at Imperial College, studying genetic factors contributing to monogenic and complex diseases using high- throughput sequencing, and she has experience of the use of high-throughput sequencing in the clinical diagnostic context in the Clinical Genetics department at Guy's and St Thomas' Hospital, London. Her current role on the Genomics England Science Team led by Professor Mark Caulfield involves working with England's Genomic Medicine Centres on delivery of the 100,000 Genomes Project, now focused primarily on analysis and reporting of results for patients with rare diseases. At Imperial College NHS Trust, she has supported delivery of the rare disease arm of the 100,000 Genomes Project at West London Genomic Medicine Centre, and is now preparing to implement the new NHS England Genomic Medicine Services.

Abstract:

Title: Cardiovascular diagnostic genomic testing

The 100,000 Genomes Project had the dual aims of investigating the utility of whole genome sequencing for diagnostic genetic testing, and initiating a research database combining genomic and phenotypic data on large patient cohorts. Over 3700 families with a cardiovascular disorder have had their genomes sequenced, and diagnostic results are being processed in the NHS Genomic Medicine Centres. As the diagnostic phase reaches its conclusion, and the research phase accelerates, NHS England has launched the national Genomic Medicine Service. Cardiologists and cardiac clinical scientists have contributed to the development of the 15 Clinical Indications for tests included in the national Genomic Test Directory, and the 12 consensus diagnostic gene panels required to deliver these tests.

Dr. Federica Montanaro has a long-standing interest in dystrophin and its associated diseases: Duchenne, Becker and X-linked muscular dystrophies. Dr. Montanaro received her PhD degree in Neurobiology from McGill University (Montreal, Canada), where her thesis on the role of dystrophin-associated proteins in neuromuscular synapse formation was awarded the Dean's Honour List and the prestigious Maclachlan prize. She then joined the laboratory of Prof. Louis Kunkel at Harvard Medical School (Boston, MA) as a Howard Hughes Medical Institute post-doctoral fellow, where she worked on dystrophic muscle regeneration and cell-therapy approaches.

In 2005, she became assistant professor at the Ohio State University and established her laboratory within the Gene Therapy Centre at Nationwide Children's Hospital (Columbus, Ohio). In 2016, she was awarded an EU Marie-Curie Re-Integration senior fellowship and joined the Dubowitz Neuromuscular Centre as senior lecturer at the UCL-Institute of Child Health (London). Her research programme uses a combination of genetic and biochemical approaches to characterize proteins that interact with dystrophin *in vivo*, with a particular interest in understanding the molecular underpinnings of cardiomyopathy in Duchenne and Becker muscular dystrophies. Her research is especially relevant to micro-dystrophin gene therapy and exon skipping treatment approaches for Duchenne muscular dystrophy.

"A fresh look at dystrophin in cardiomyopathy"

Dystrophin is a critical cytoskeletal protein in skeletal and cardiac muscle cells. Mutations affecting dystrophin expression or function lead to Duchenne or Becker muscular dystrophies, both characterized by progressive loss of ambulation and early mortality due to cardio- respiratory failure. In the early 1990's, the dystrophin-associated protein complex (DAPC) was discovered, leading to the identification of new genes linked to myopathies. From these studies, a unified picture has emerged where dystrophin and the DAPC are present in all striated muscles where they are required to preserve the membrane integrity of muscle cells. This model implies that dystrophin assembles the same protein complex and performs the same functions in cardiac and skeletal muscles. However, this assumption does not explain the existence of dystrophin mutations that preferentially or even exclusively cause cardiac disease. This prompted us to re-examine the protein complexes assembled by dystrophin in cardiac and skeletal muscles. We discovered the existence of a cardiac-specific DAPC that includes proteins previously implicated in long-QT syndrome, arrhythmias, dilated cardiomyopathy, and congenital generalized lipodystrophies. These findings are reshaping our view of the role of dystrophin in the heart and have important implications for cardiac treatment development for Duchenne and Becker muscular dystrophies.

Keywords: Duchenne muscular dystrophy, Becker muscular dystrophy, dystrophin, caveolae

Dr. James Ware is a Reader in Genomic Medicine at Imperial College London and the MRC London Institute of Medical Sciences, and Consultant Cardiologist at Royal Brompton and Harefield Hospitals. He graduated from the University of Cambridge, trained clinically in London & Geneva, and pursued research training at Imperial College London, Harvard Medical School, and the Broad Institute of MIT & Harvard.

James' research aims to understand the impact of genetic variation on the heart and circulation, and to use genomic information for precision medicine. Clinical interests include the management of Inherited Cardiac Conditions, and the broader application of genetics and genomics to healthcare.

Interpreting variation in Titin in health and disease

Titin is the largest protein in the human body, and a key component of the sarcomere in all striated muscle. Genetic variation in the gene encoding Titin is almost ubiquitous, and presents an enormous clinical challenge. This talk will address the role of Titin in human cardiovascular diseases, the challenges of interpreting genetic variation in *Titin*, and potential opportunities for genome-stratified medicine.

Professor Dr. Julie de Backer

Department of Medical Genetics

Gent University Hospital
Gent, Belgium

Clinical geneticist with a special interest in heritable disorders of connective tissue. Lead the International Consortium on Marfan Syndrome, widely acknowledged as the Gent diagnostic criteria.

'Genomic insights in thoracic aortic disease'

Heritable Thoracic Aortic Disease (HTAD) can clinically be subdivided into syndromic and nonsyndromic forms.
Mutation detection rates are substantially higher in syndromic forms (>90% versus 10-15%) but in both cases, significant genetic heterogeneity is notable. Based on increasing insights on the role of the various genes and gene pathways in the pathophysiology of HTAD, disease severity prediction is improving, which should lead to better management.
The following aspects will be covered in this presentation:

1. Inter-gene differences: although disease severity prediction on the individual level will remain challenging, some insights are emerging from large cohort studies and will be discussed
2. Looking at individual genes, some relevant differences in clinical expression and possibly also in response to treatment between different variant types have been reported and are worth further exploration.
3. Two aspects relevant to the complex interaction between genes and environment in the setting of HTAD will be discussed: sex and pregnancy
4. Finally, based on the improved knowledge on the pathogenesis of HTAD, some controversies and new prospects for treatment will be discussed

Keywords: heritable thoracic aortic disease; gene-based risk; gene-based management

Ms. Morven Dunn is incredibly privileged to work for BHF as a CVD Clinical Development Coordinator for the last 5 years, working with health care professionals, commissioners and policy makers to influence improvement in the service provision and care for people living with or at risk of CVD.
Morven has worked in a variety of cardiology nursing roles over the last 25 years including: arrhythmia, rapid access chest pain clinics, cardiac rehabilitation, cardiac ICU and CCU. Throughout
her nursing carer she has had a passion for teaching and education and has been a visiting lecturer in Caledonian University for the last 15 years and previously worked as a l lecturer at a further education college. She also was honoured to be involved in an innovative programme in primary care developing the role of CVD Nurse in General Practice.

"The Miles Frost Hypertrophic Cardiomyopathy Prevention- a model for Preventive (Community/Public Health) Cardiology"

The Miles Frost Fund aims to raise £1.5 million to help make genetic testing available to all families affected by the deadly heart condition hypertrophic cardiomyopathy (HCM). Miles Frost died suddenly of HCM in July 2015 when he was just 31.

In Miles' memory, the Frost family has set up the Miles Frost Fund to raise money for the British Heart Foundation (BHF) to ensure that genetic testing for immediate family members of those affected by HCM is available nationwide. This will help more people to be diagnosed with the deadly condition so it can be treated before it's too late.

This presentation will provide an overview of how the fund has been utilised across the UK, focussing on where and how the monies has enabled funded sites to invest in their services. It will describe the challenges, barriers and emerging themes observed and discuss the evaluation findings with the audience

Professor Patricia Munroe is Professor of Molecular Medicine at Queen Mary University of London. She obtained BSc and MSc degrees from the National University of Ireland Galway, and obtained her PhD from the University of London. Her main research interest is the genetics of cardiovascular risk factors for understanding biology, disease prediction and translation to personalised medicine. She is a co- founder of the International Consortium for Blood Pressure (ICBP) and has co-led several high-profile projects over the past decade leading to the discovery of over 1000 blood pressure loci. She is also a member of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium co-leading several projects including genetic studies of electrocardiogram markers associated with risk of cardiac arrhythmias and sudden cardiac death. She has published over 200 original publications and her work is funded by the MRC, BHF and NIHR.

Tom Lumbers MRCP PhD
Tom is Honorary Consultant Cardiologist at Barts Heart Centre, HDR UK Fellow at UCL, and a Visiting Scientist at the Broad Institute of Harvard and MIT. Tom's research focuses on defining the genetic architecture of heart failure and left ventricular dysfunction. He co-founded the HERMES Consortium, an international collaboration in heart failure genetics and co-leads the phenotype group for BigData@Heart, an EU public-private consortium (www.bigdata-heart.eu).

Defining cardiovascular diseases at scale using multimodal electronic health records

Electronic health records (EHRs) provide a rich source of information on cardiovascular diseases at scale, however, data is variably structured, fragmented and annotated using different coding systems. Unlocking the value of large genomic biobanks, linked to EHR, to define the genetic determinants of disease relies upon robust, reproducible, and multi-modal phenotype definitions. Here, we describe a UK EHR framework for the development, validation and disease phenotypes with translational applications in research and practice.

Keywords: Electronic health records, heart failure, genomics

"Hypertrophic cardiomyopathy and pregnancy outcomes"

Pooja Sikka[1], Vanita Suri[1], Neelam Aggarwal[1], Seema Chopra[1], Ajay Bahl[2]

1 Department of obstetrics and gynaecology, 2 Department of cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh.

Background:

Hypertrophic cardiomyopathy (HCM) is a complex, genetic cardiac disorder, the exact incidence of which in pregnancies is unknown. Both obstetricians and cardiologists face the difficult issue of managing HCM in pregnancy as controversies still persist regarding risks associated with pregnancy and delivery. HCM is considered a WHO class 2 and 3 risk, implying thereby that there is a moderate risk of morbidity in most women and a significant risk for few. To date, pregnancy outcome data for these patients is scarce. Though small studies have reported no deaths associated with pregnancy in HCM, some have highlighted several maternal complications. Widespread use of echocardiography and both genetic and clinical screening of families with HCM has led to a higher number of women being diagnosed as HCM nowadays. We report the experience of pregnancies with HCM in a tertiary care hospital in North India.

Aims:

To study maternal and fetal outcomes in women with hypertrophic cardiomyopathy and to identify factors that may influence pregnancy outcomes.

Methods:

This was a retrospective analysis of registry data. All patients with hypertrophic cardiomyopathy registered in the cardio-obstetric clinic as well as hypertrophic cardiomyopathy cohort in department of cardiology between January 2004 and June 2019 were included in the study. Clinical data, mode and time of delivery, antenatal, intrapartum and postpartum complications and fetal outcomes were analyzed. Severity of left ventricular hypertrophy, left ventricular outflow tract obstruction, arrhythmias were also be recorded and correlated with pregnancy outcomes. Risk factors contributing to adverse maternal and fetal outcomes were studied.

Results:

There were 16 pregnancies in 8 women (range 1-4) with HCM during the study period. Mean age was 24.75±3.51 years. Mean left ventricular wall thickness was 20±2.5 mm. Two patients became symptomatic for first time during first pregnancy and were diagnosed to have HCM whereas 6 women were known to have HCM prior to pregnancy. Two patients had left ventricular outflow tract obstruction (LVOTO) whereas on developed LVOTO only during her fourth pregnancy. One of these underwent alcohol septal ablation after the first of 3 pregnancies. Five women did not have LVOTO. Two women had restrictive physiology. Four were normal vaginal delivery, 8 had lower section caesarean section, all for fetal indication and 4 underwent medical termination of pregnancy. Increase in symptoms to NYHA class III/IV occurred in 3 pregnancies while 1 patient had aggravation of symptoms soon after caesarean section. There was no increase in symptoms in 12 pregnancies. Of the 7 pregnancies in women with LVOTO, 2 had aggravation of symptoms whereas aggravation of symptoms occurred in 2 of 9 pregnancies which did not have LVOTO. Of 2 women with restrictive physiology became symptomatic at as early as 24 weeks of gestation. Her symptoms rapidly progressed and by 26 weeks she went into

heart failure with pulmonary oedema and pericardial effusion. She had an intrauterine fetal death at this time. She was managed with beta blockers and diuretics. Induction of labor was done with pitocin for pregnancy termination at 28 weeks. She delivered uneventfully and there was a gradual improvement in her symptoms after delivery. Another patient had intrauterine fetal death at 16 weeks of gestation. This was not associated with increase in symptoms related to HCM.

Conclusions:

Pregnancy is usually well tolerated in women with HCM, though severe symptoms occur in 25% pregnancies which improve with delivery. Most pregnancies in women with LVOTO are well tolerated. HCM patient with restrictive physiology developed heart failure with resultant adverse pregnancy outcome.

"Whole genome and transcriptome sequencing of post-mortem cardiac tissues from sudden cardiac death victims identifies a gene regulatory variant in *NEXN*"

S. B. Jacobsen[1], J. D. Andersen[1], L. C. Trudsø[1], M-L. Kampmann[1], J. Banner[2], N. Morling[1]*

[1] Section of Forensic Genetics, Department of Forensic Medicine, Faculty of Health and Medical Sciences, University of Copenhagen
[2] Section of Forensic Pathology, Department of Forensic Medicine, Faculty of Health and Medical Sciences, University of Copenhagen; *E-mail address: stine.b.jacobsen@sund.ku.dk TEL: +45 35326916

Sudden cardiac death (SCD) is a devastating event that constitutes a diagnostic challenge in forensic pathology, especially in cases with structurally normal hearts. Due to the high heritability of diseases underlying SCD, post-mortem genetic analyses, so-called molecular autopsies, have been an expanding field of research in recent years. The vast majority of studies have focused on genetic variation in coding regions of cardiac genes, resulting in the identification of pathogenic variants in up to 30% of SCD cases. However, much remain unknown about potential associations between SCD and variants in non-coding regions of the genome.

In this study, we performed whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) to explore the potential association between genetic variants in non-coding regulatory regions and gene expression levels. WGS was performed using frozen tissue and WTS using formalin-fixed, paraffin-embedded (FFPE) cardiac tissue from nine sudden arrhythmic death syndrome (SADS) and three sudden unexplained death in infancy (SUDI) deceased individuals.

We identified a variant in the promoter region of the gene *NEXN*, c.-194A>G, that was found to be statistically significantly ($p < 0.05$) associated with an approximately 10 time decreased expression of *NEXN* and cardiac hypertrophy. This study highlights the potential of using WTS to evaluate the effect of genetic variation in non-coding regulatory regions.

Keywords: Sudden cardiac death · Molecular autopsy · Whole genome sequencing · Whole transcriptome sequencing · Formalin-fixed, paraffin-embedded tissue · NEXN

Discovery of a novel putative pathogenic truncating variant in MYH7 in Egyptian HCM patients

Mona Allouba[1,2*], Yasmine Aguib[1,2*], Alaa Afify[1], Aya Galal[1], Roddy Walsh[2,5], Pantazis Theotokis[2], Nicola Whiffin[2], Sarah Halawa[1,3], Ahmed Elguindy[1,2], Shehab Anwer[1], Stuart A Cook[2,4], Paul J Barton[2], James Ware[2], Magdi Yacoub[1,2,6]

[1]Aswan Heart Centre, Egypt; [2]NHLI, Imperial College London, London, UK; [3]The American University in Cairo, Egypt; [4]National Heart Centre Singapore, Singapore; [5]Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Netherlands; [6]Harefield Heart Science Centre, UK

Abstract

Introduction: Hypertrophic Cardiomyopathy (HCM) is an inherited disease characterised by genetic and phenotypic heterogeneity. The genetic determinants of HCM in Egypt have not been studied, particularly in relation to controls.

Aim: To define the genetic architecture of Egyptian HCM (AhcHCM) patients and elucidate disease mechanisms of novel putative pathogenic variants.

Methods: Prospective AhcHCM patients (n=516) and Egyptian Healthy Volunteers (EHVols) (n=400) were recruited to Aswan Heart Centre for clinical phenotyping and genetic testing. Samples were sequenced for 174 genes implicated in inherited cardiac conditions (Illumina). The excess of rare variation (gnomAD filtering allele frequency <= $4x10^{-4}$) in each HCM gene in the AhcHCM cohort over EHVols was calculated.

Results and Conclusions: A significant burden of a novel truncating variant in MYH7 (MYH7tv) was observed in the AhcHCM cohort over EHVols ($p <= 0.002$). To elucidate the underlying mechanism of MYH7tv we are using functional genomics approaches to characterise induced pluripotent stem cell-derived cardiomyocytes generated from patients' myocardial tissues harbouring the variant. In contrast to current knowledge, we hypothesize that the mutant MYH7 transcript escaped nonsense mediated decay to act as a disease-causing protein. Characterisation of the novel MYH7tv may provide deeper mechanistic insights and contribute to precision in HCM clinical practice.

Keywords: Cardiovascular Disease, Novel variant, Precision Medicine

Professor Sahar Mansour, MD FRCP
Consultant in Clinical Geneticist
St. George's Hospital Medical School
University of London, UK

Sahar is the Lead Clinical Geneticist for genetic dermatology . Her special interest includes primary lymphatic disorders.

The Egyptian Collaborative Cardiac Genomics (ECCO-GEN): Defining a Healthy Volunteer Cohort

Yasmine Aguib[1,2], Mona Allouba[1,2,3]*, Alaa Afify[1]*, Sarah Halawa[1,4], Mohamed ElKhateb[1], Marina Sous[1], Aya Galal[1], Eslam Abdelrahman[1], Nairouz Shehata[1], Amr El Sawy[1], Mohamed Maghawry[1], Shehab Anwer[1], Omnia Kamel[1], Wessam El-Mozy[1], Hadir Khedr[1], Ahmed Kharabish[1], Nagwa Thabet[1], Pantazis Theotokis[2,3], Rachel Buchan[2,3], Risha Govind[2,3], Nicola Whiffin[2,3,8], Roddy Walsh[2,3,7], Heba Aguib[1], Ahmed Elguindy[1,2], Stuart A Cook[2,3,5,6], Paul J Barton[2,3], James Ware[2,3,8], Magdi Yacoub[1,2,9].*

**authors contributed equally*
[1] Aswan Heart Centre, Aswan, Egypt
[2] National Heart and Lung Institute, Imperial College London, London, UK
[3] Cardiovascular Research Centre, Royal Brompton Hospital and Harefield NHS Foundation Trust, London, UK
[4] The American University in Cairo, AUC Ave, Cairo, Egypt
[5] National Heart Centre Singapore, Singapore, Singapore
[6] Duke-National University of Singapore, Singapore, Singapore
[7] Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Amsterdam, Netherlands
[8] MRC London Institute of Medical Sciences, Imperial College London, London, UK
[9] Harefield Heart Science Centre, Harefield, Middlesex, United Kingdom

Abstract

Introduction: Integration of comprehensive genomic and phenotypic data from diverse ethnic populations offers unprecedented opportunities towards advancements in precision medicine and novel diagnostic technologies. Current reference genomic databases, such the Genome Aggregation Database (gnomAD), lack genetic data from the North African population. To ameliorate this knowledge gap, the Egyptian Collaborative Cardiac Genomics (ECCO-GEN) Project launched a study comprising 1000 individuals free of cardiovascular disease (CVD).

Aim: To define the genetic landscape of the understudied Egyptian population to support future studies in CVD and population genetics.

Methods: Egyptian healthy volunteers (EHVols) were recruited to Aswan Heart Centre for clinical- and genetic testing using a targeted sequencing panel of 174 genes associated with inherited cardiac conditions. Variants were interpreted in accordance with the ACMG guidelines.

Results: We present the first 391 EHVols recruited to establish a pilot phenotyped control cohort. We identified 1,262 variants in 27 cardiomyopathy genes of which 15.1% were not captured in current global (gnomAD) and regional (GME) genetic reference databases.

Conclusions: This study provides preliminary insights into genetic variation of the multi-ethnic Egyptian population. Expanding the ECCO-GEN project and integrating ancestry-specific genetic and phenotypic data will deepen our understanding of African diversity, which is crucial for precision medicine.

Keywords: 100 Egyptian genomes, cardiovascular disease, Africa

"Loss-of-function variants in myocardin cause congenital megabladder in humans and mice"

Arjan C. Houweling[1,19*], Glenda M. Beaman[2,3,19], Alex V. Postma[4,5,19], T. Blair Gainous[6], Klaske D. Lichtenbelt[7], Francesco Brancati[8,9], Filipa M. Lopes[10], Ingeborg van der Made[11], Abeltje M. Polstra[1,12], Michael L. Robinson[13], Kevin D. Wright[13], Jamie M. Ellingford[2,3], Ashley R. Jackson[14], Eline Overwater[1,5], Rita Genesio[15], Silvio Romano[9], Letizia Camerota[16], Emanuela D'Angelo[17], Elizabeth J. Meijers-Heijboer[1], Vincent M. Christoffels[4], Kirk M. McHugh[14], Brian L. Black[6], William G. Newman[2,3,20], Adrian S. Woolf[10,18,20], Esther E. Creemers[11,20*]

[1]Department of Clinical Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

[2]Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology Medicine and Health, University of Manchester, UK.

[3]Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

[4]Department of Medical Biology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Academic Medical Center, the Netherlands

[5]Department of Clinical Genetics, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Academic Medical Center, the Netherlands.

[6]Cardiovascular Research Institute, University of California, San Francisco, CA, USA

[7]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

[8]Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata, IDI-IRCCS, Rome, Italy

[9]Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy.

[10]Division of Cell Matrix Biology and Regenerative Medicine, School of Biological Sciences, Faculty of Biology Medicine and Health, University of Manchester, UK.

[11]Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Academic Medical Center, Amsterdam, the Netherlands.

[12]Laboratory Genetic Metabolic Diseases, Departments of Clinical Chemistry and Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

[13]Department of Biology, Miami University, Oxford, Ohio, USA

[14]Center for Clinical and Translational Research, The Research Institute, Nationwide Children's Hospital, Columbus, Ohio, USA.

[15]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy

[16]Medical Genetics Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

[17]Pathology Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

[18]Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

[19]These authors contributed equally

[20]These authors jointly supervised this work

*Corresponce: a.houweling@vumc.nl or e.e.creemers@amc.uva.nl

Abstract

Myocardin (MYOCD) is the founding member of a class of transcriptional co-activators that bind serum response factor to activate gene expression programs coding for contractile and other cytoskeletal proteins critical in smooth- and cardiac muscle development. Insights into the molecular functions of MYOCD have been obtained from cell culture studies and, to date, our *in vivo* knowledge about MYOCD comes exclusively from experimental animals. For example, expression of dominant negative *Myocd* disrupts myocardial differentiation in embryonic frogs, while *Myocd* null mice die midgestation with failed vascular smooth muscle (SM) cell differentiation. Here, we define a devastating and often lethal human congenital disease associated with inheritance of pathogenic *MYOCD* variants, with 14 affected

individuals in four families. This disease manifests as a massively dilated urinary bladder, or megabladder, with a disrupted SM wall. These human results are supported by evidence of megabladder in two distinct mouse models with reduced *Myocd* levels. Together, these findings highlight a vital role for MYOCD in mammalian organogenesis. In conclusion, we demonstrate for the first time that variations in MYOCD result in human disease, and propose that loss-of-function variants in MYOCD cause semi-dominant congenital megabladder. This has important implications for genetic counseling of families with congenital megabladder, sheds new light on bladder development, and expands the pathophysiological spectrum of inherited SM disorders.

Dr Siv Fokstuen, MD

Dr Siv Fokstuen is a clinical geneticist working as Associate Professor at the Institute of Medical Genetics of the University Hospitals in Geneva, and as senior consultant at the University Heart Center in Zurich, Switzerland. Her main academic interest is focused on mendelian cardiac disorders, in particular on hypertrophic cardiomyopathy.

Challenge of variant classification in cardiovascular medicine: The example of hypertrophic cardiomyopathy

S. Fokstuen[1], Ch. Gruner[2], H. Hammer[2], M. Guipponi[1], E. Hammar[1], M. Beghetti[3], Ph. Meyer[4], M. Abramowicz[1], J.-L. Blouin[1]

[1]Service of Genetic Medicine, University Hospitals of Geneva, Geneva, Switzerland
[2]Department of Cardiology, Herzzentrum University Hospital Zürich, Zürich, Switzerland
[3]Pediatric Cardiology, University Hospitals of Geneva, Geneva, Switzerland
[4]Cardiology, University Hospitals of Geneva, Geneva, Switzerland

High throughput sequencing technology has made it possible to analyze all known hypertrophic cardiomyopathy (HCM) genes in parallel. As a result variants of unknown clinical significance (VUS) are increasingly detected. The situation is aggravated by the fact that apart from the well known described main HCM genes, many diagnostic laboratories perform large panel analysis including genes of other cardiomyopathy subtypes and/or genes whose evidence is only limited. At the University Hospitals of Geneva we currently analyze by targeted exome sequencing 65 genes responsible for all subtypes of cardiomyopathies. We present here the results of 55 unrelated HCM probands. At least one pathogenic or likely pathogenic variant was found in 48 % (26/54). *MYBPC3* gene variants accounted for 77 % (20/26). The other 6 variants were found in *MYH7* (N=2), *TPM1* (n=1), *MYPN* (n=1), *TNNI3* (n=1), and *TNNT2* (n=1). Six of the 26 probands had in addition a second variant of unknown clinical significance. In 22 % (12/54) only a VUS was identified and in 29 % (16/54) no variant of clinical significance was found. The ACMG guidelines for variant classification are challenging for patients with HCM, especially due to the incomplete penetrance.

SELECTED ORAL PRESENTATIONS

1. "Heart failure, severe arrhythmia and sudden cardiac death in Marfan syndrome and related heritable thoracic aortic diseases"

Anthony Demolder[1], Laura Muiño Mosquera[1,2], Laurence Campens[3], Julie De Backer[1,3]

[1]Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium.
[2]Department of Pediatrics, Division of Pediatric Cardiology, Ghent University Hospital, Ghent, Belgium.
[3]Department of Cardiology, Ghent University Hospital, Ghent, Belgium.
Contact person: Anthony Demolder
Email: anthony.demolder@ugent.be
Tel: 0032 472 08 51 01

Brief summary:

Background: Marfan syndrome (MFS) and related heritable thoracic aortic diseases (HTAD) are well-known for their aortic complications. Heart failure, severe arrhythmia and sudden cardiac death are less known in this setting but have been reported.

Methods: To define the prevalence of severe arrhythmia, heart failure and sudden cardiac death, we conducted a retrospective, single-center study of adults and children with MFS and related HTAD. The primary composite endpoint was defined as heart failure (HF), heart transplantation (HTx), severe arrhythmia (SA) or sudden cardiac death most likely due to arrhythmia (SCD). The secondary endpoint was death due to any cause.

Results: Overall, 154 patients with MFS and 32 patients with related HTAD underwent regular follow-up between 2004 and 2019. During follow-up, 8 patients reached the primary composite endpoint (3 SCD, 2 SA, 1 HF and 2 HTx). Of these 8 patients, 7 had MFS and 1 had a related HTAD (SMAD3 pathogenic variant). In total, 11 patients died during follow-up (10 MFS and 1 related HTAD). Cardiovascular causes of death in MFS were aortic dissection (3/10), SCD (2/10), SA (1/10) and HF (1/10). Other causes of death were cancer (1/10) and unknown (2/10). The only deceased patient in the related HTAD group died due to SCD.

Background:

Marfan syndrome and related heritable thoracic aortic diseases (HTAD) are well-known for their aortic complications resulting in prophylactic aortic surgery, aortic dissection and death. Life expectancy has improved due to careful follow-up and prophylactic treatment. Heart failure and arrhythmia are less known in this setting but have been reported, also as significant causes of death in these patients.

Purpose

To define the prevalence of severe arrhythmia, heart failure and sudden cardiac death in patients with Marfan syndrome and related HTAD managed according to standard recommendations.

Methods

We conducted a retrospective, single-center study of adults and children with Marfan syndrome (MFS) and related heritable thoracic aortic diseases (HTAD). Patients with confirmed pathogenic variants in the causative genes *FBN1, TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD3* and *ACTA2* underwent regular clinical follow-up with electrocardiography, echocardiography and cardiovascular MRI. The primary composite endpoint was defined as heart failure (HF), heart transplantation (HTx), severe arrhythmia (SA) or sudden cardiac death most likely due to arrhythmia (SCD). The secondary endpoint was death due to any cause.

Results

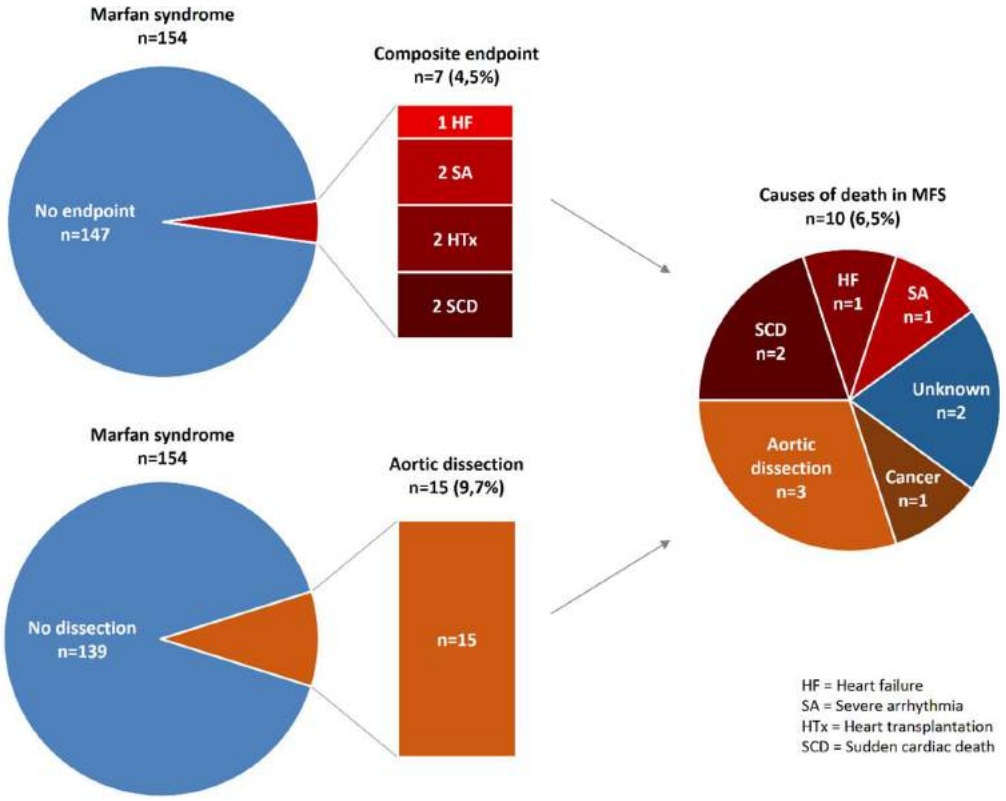
Overall, 154 patients with Marfan syndrome (aged 35 [23-49] years, 51% women) and 32 patients with related HTAD (aged 41 [25-57] years, 50% women) underwent regular follow-up between 2004 and 2019. Aortic involvement (Z-score ≥2) was observed in 129 patients (83,7%) in the MFS group and 21 patients (65,6%) in the HTAD group. During follow-up, 8 patients (aged 30 [19-50], 38% women) reached the primary composite endpoint (3 SCD, 2 SA, 1 HF and 2 HTx). Of these 8 patients, 7 had MFS and 1 had a related HTAD (SMAD3 pathogenic variant). In total, 11 patients died during follow-up (10 MFS and 1 related HTAD). Cardiovascular causes of death in MFS were aortic dissection (3/10), SCD (2/10), SA (1/10) and HF (1/10). Other causes of death were cancer (1/10) and unknown (2/10). The only deceased patient in the related HTAD group died due to SCD.

Conclusion

Heart failure, severe arrhythmias and sudden cardiac death are rare in patients with MFS and related HTAD managed according to the standard recommendations. Despite their infrequency, they constitute a relevant cause of death. To identify predisposing factors associated with these rare, yet severe cardiac complications, a multicenter joint initiative is needed.

Key words: Marfan, HTAD, heart failure, arrhythmia, SCD

Figure 1: Heart failure, severe arrhythmia and sudden cardiac death observed in MFS



2. "Atypical *COL3A1* variants (glutamic acid to lysine) cause vascular Ehlers-Danlos Syndrome with a consistent phenotype of tissue fragility and skin hyperextensibility."

Neeti Ghali[1*], MD, Duncan Baker[2], FRCPath (Dip), BSc, Angela F Brady[1], PhD, Nigel Burrows[3], MD, FRCP, Elena Cervi[4], PhD, Deirdre Cilliers[5], MD, Michael Frank[6], MD, Dominique P Germain[7], MD, PhD, David JS Hulmes[8], PhD, Marie-line Jacquemont[9] , MD, Peter Kannu[10], FRACP, Henrietta Lefroy[5], MRCP, Anne Legrand[11] , PharmD, F. Michael Pope[12], MD, Lisa Robertson[13], MRCP, Anthony Vandersteen[14], PhD, Kate von Klemperer[15], MRCP, Renarta Warburton[2], BSc, MSc, Margo Whiteford[16] BSc, FRCP and Fleur van Dijk, MD, PhD.[1]

[1] *Ehlers-Danlos Syndrome National Diagnostic Service London, North West Thames Regional Genetics Service, London North West Healthcare University NHS Trust, Harrow, Middlesex, UK*
[2] *Connective Tissue Disorders Service, Sheffield Diagnostic Genetics Service, Sheffield, UK*
[3] *Department of Dermatology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*
[4] *Centre of Inherited Cardiovascular Diseases, Great Ormond Street Hospital NHS Foundation Trust, London, UK*
[5] *Oxford Centre for Genomic Medicine, Oxford University NHS Foundation Trust, Oxford, UK*
[6] *AP-HP Hopital European Georges Pompidou, Departement de Genetique, Sercie de Medecine Vasculaire et Centre de Reference des Maladies Vasculaires Rares, Paris, France*
[7] Division of Medical Genetics, University of Versailles, Paris-Saclay University, 78180 Montigny, France
[8] *UMR5305, CNRS / Université Claude Bernard Lyon 1, Lyon, France*
[9] Medical Genetics Unit, CHU La Réunion, Saint-Pierre, France
[10] *Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada*
[11] *Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Centre de Référence des Maladies Vasculaires Rares, Paris, France*
[12] *Department of Dermatology, Chelsea & Westminster Hospital NHS Foundation Trust, London, UK*
[13] *Department of Clinical Genetics, Aberdeen Royal Infirmary, Scotland*

[14] *Maritime Medical Genetics Service, IWK Health Centre, Halifax, Nova Scotia, Canada*
[15] *Department of Cardiology, St Barthlomew's Hospital, London, UK*
[16] *Clinical Genetics West of Scotland Regional Genetics Service, Queen Elizabeth University Hospital Glasgow, UK*

Name of presenter **Dr. Neeti Ghali**

ABSTRACT

The Ehlers-Danlos syndromes (EDS) are a group of rare inherited connective tissue disorders. Vascular EDS (vEDS) is caused by pathogenic variants in *COL3A1*, most frequently glycine

substitutions. We describe the phenotype of the largest series of vEDS patients with glutamic acid to lysine substitutions (Glu>Lys) in *COL3A1* which were all previously considered to be variants of unknown significance.

Clinical and molecular data for seven families with three different Glu>Lys substitutions in *COL3A1* were analysed.

These Glu>Lys variants were reclassified from variants of unknown significance to either pathogenic or likely pathogenic in accordance with ACMG guidelines. All individuals with these atypical variants exhibited skin hyperextensibility as seen in individuals with Classical EDS and Classical-like EDS and evidence of tissue fragility as seen in individuals with vEDS.

The clinical data demonstrate the overlap between the different EDS subtypes and underline the importance of next-generation sequencing gene panel analysis. The three different Glu>Lys variants point towards a new variant type in *COL3A1* causative of vEDS which has consistent clinical features. This is important knowledge for *COL3A1* variant interpretation. Further follow-up data are required to establish the severity of tissue fragility complications compared to patients with other recognized molecular causes of vEDS.

[198 words]

KEYWORDS

Ehlers-Danlos Syndrome; *COL3A1*; Vascular EDS

3. "Genome sequencing for inherited cardiac conditions: analysis of 201 cardiovascular patients recruited through the 100,000 Genomes project by the West of England and South West NHS Genomic Medicine Centres."

Rebecca Whittington[1], Carolyn Dent[1], Hannah Robinson[2], Julie Evans[1], Mary Gable[1], Karen Low[5], Alan Donaldson[5,6], Ruth Newbury-Ecob[4,5], Claire Turner[2], Martina Muggenthaler[2]; Catherine Carpenter-Clawson[4], Aileen McCloughlin[4], Ana Juett[3], Graham Stuart[7], Sian Ellard[2,3] and Maggie Williams[1].

[1]North Bristol NHS Trust, [2]Royal Devon & Exeter NHS Foundation Trust, [3]South West NHS Genomic Medicine Centre, [4]West of England NHS Genomic Medicine Centre, [5] University Hospitals Bristol NHS Trust, [6]Gloucestershire Royal Hospital, [7] Bristol Heart Institute.

Contact email: Rebecca.whittington@nbt.nhs.uk; Contact telephone: 0117 414 6175

Key words: 100,000 genomes; inherited cardiac conditions; whole genome sequencing

The West of England and South West NHS Genomic Medicine Centres have recruited 276 cardiovascular index cases to the 100,000 Genomes Project, representing 7.4% of the total cardiac cohort of 3728 cases. Many patients have previously undergone multiple rounds of genetic testing without a diagnosis.

Initial analysis of whole genome sequencing data is on phenotype driven (HPO) assigned gene panels curated, through PanelApp. This identified 10 pathogenic /likely pathogenic or candidate variants. Additional analysis searching for *de novo* and biallelic recessive variants outside of applied gene panels was performed for cases with no tiered variants and identified 2 additional diagnoses.

Analysis identified a hemizygous *BGN* splice variant and *FLNC* nonsense variant; ending the diagnostic odyssey for these patients. A gene-agnostic approach adapted from an in-house trio exome pipeline, identified bi-parental variants in *PPP1R13L*, not included in the DCM panel due to limited literature evidence; additional cases demonstrating gene-disease association were identified through GeneMatcher. The importance of timely updating of gene-panels in PanelApp is highlighted by a *NOTCH1* missense variant, reported as likely pathogenic by in-house congenital heart defect panel testing, but not highlighted by the 100,000 genomes variant tiering process.

4. "Major Genetic Contributors to Nonsyndromic Tetralogy of Fallot."

Dr. Richard Monaghan, PhD., Research Associate, University of Manchester. Dr. Donna Page, PhD., Lecturer, Manchester Metropolitan University.Dr. Simon Williams, PhD., Bioinformatician, University of Manchester. Prof. Bernard Keavney, BM, BCh, DM, FRCP, British Heart Foundation Professor of Cardiovascular Medicine and Consultant Cardiologist, Central Manchester University Hospitals NHS Trust.

Abstract

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. Rare genetic variants have been identified as important contributors to the risk of congenital heart disease, but relatively small numbers of TOF cases have been studied. We used whole exome sequencing to assess the prevalence of unique, deleterious variants in the largest cohort of nonsyndromic TOF patients reported to date. The presence of such variants was defined by their absence in the Genome Aggregation Database and bioinformatic prediction of their deleterious effect on function. The enrichment of variants in two genes, *NOTCH1* and *FLT4*, surpassed thresholds for exome-wide significance ($P<5\times10^{-8}$) after correction for multiple comparisons. *NOTCH1* was most frequently found to harbour unique, deleterious variants (4.5%; 95% CI, 3.2%– 6.1%). Three *NOTCH1* variants were subjected to functional evaluation, and two showed a reduction in Jagged1-induced NOTCH signalling. *FLT4* variants were found in 2.4% (95% CI, 1.6%–3.8%) of our cohort. In addition, variants in the well-established TOF gene, *TBX1*, and the genes were also significantly enriched. Our study underlines the importance of sequencing large cohorts of CHD cases in order to further discover their genetic basis.

Key words: congenital heart disease, exome sequencing, Tetralogy of Fallot

5. "Identifying Long QT syndrome patients in primary care: A population- based case control study"

WRH Evans*, RK Akyea, N Qureshi, J Kai, SF Weng

LQTS is an inherited cardiac arrhythmic condition that predisposes patients to syncope and sudden cardiac death. Identification to enable treatment can substantially reduce this risk.

Aim: To identify clinical features which precede diagnosis of Long QT syndrome (LQTS) in primary care and use these to develop a predictive model.

Method: We identified a cohort of 1495 patients with a diagnosis of LQTS from a database of primary care electronic records (CPRD). Each case was matched to 5 controls, accounting for covariates by propensity matching, and clinical features were identified that occurred prior to diagnosis. Multivariable logistic modelling was performed to develop a predictive tool.

Results: A range of clinical features occurring with greater frequency in LQTS patients were identified including: Palpitations (2.13 (1.73,2.62)); epilepsy (1.98 (1.32, 2.98)); irritable bowel syndrome (1.85 (1.46, 2.33)); hypertension (1.83 (1.58,2.11) (OR (95% CI)). A total of 18 clinical features were incorporated into the predictive model with an area under the ROC curve of 0.7004.

This is the first study to assess how patients with LQTS present to primary care, with a range of both expected and unexpected clinical features found. This study demonstrates the potential of primary care records to identify patients with an increased likelihood of having a rare disease.

Key words: Genetics, primary care, inherited cardiology, LQTS

PRISM group, Division of Primary care, University of Nottingham.
William.Evans1@nottingham.ac.uk, 07850732023

6. "Biallelic *PPP1R13L*-associated paediatric dilated cardiomyopathy: expanding the phenotypic spectrum"

C.L. Turner[1], H.K. Robinson[2], L. Mallin[2], C. Armstrong[3], D. Mabin[4], E. Zaklyazminskaya[5], I. Povolotskaya[6], Y. Surikova[7], P.J. Benke[8,9], M.R. Chrisant[9], C.C. Marboe[10], M Mcdonald[11], K. Agre[12], D. Deyle[12], K M. Balashova[6], V. Kaimonov[6], N. Shirokova[6], E. Pomerantseva[6], K. McWalter[13], G. Douglas[13], S. Ellard[2,14]

(1) Peninsula Clinical Genetics Service, Department of Clinical Genetics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

(2) Molecular Genetics Department, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

(3) Paediatric Cardiac Service, Bristol Royal Hospital for Children, Bristol, UK

(4) Department of Paediatrics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK Centre of

(5) Centre of Syncope and Cardiac Arrhythmias in Children and Adolescents, Moscow, Russia

(6) Genetics and Reproductive Medicine "Genetico", Moscow, Russia

(7) B.V. Petrovsky Russian Scientific Center of Surgery, Moscow, Russia

(8) Charles E. Schmidt College of Medicine, Florida Atlantic University, Florida, USA

(9) Joe DiMaggio Children's Hospital, Hollywood, Florida, USA

(10) Department of Pathology and Cell Biology, Columbia University Medical Centre, New York, USA

(11) Division of Medical Genetics, Department of Pediatrics, Duke University, Durham, NC, USA

(12) Mayo Clinic, Department of Clinical Genomics, Rochester, Minnesota, USA

(13) GeneDx Inc., Gaithersburg, Maryland, USA

(14) Institute of Biomedical and Clinical Science, College of Medicine and Health, Exeter, UK

claire.turner12@nhs.net 01392 405749

Paediatric dilated cardiomyopathy (DCM) has a reported annual incidence of 0.57 cases per 100,000. Although rare, it is associated with significant morbidity and mortality, being a common reason for heart transplantation and sudden death. It is multifactorial but a proportion of cases have a genetic aetiology with significant heterogeneity. Genomics England PanelApp currently includes around 50 causative genes, but exome (ES) or genome sequencing (GS) is important for detecting emergent genetic causes.

ES, utilised recently to investigate a single consanguineous family in which five children had DCM and variable ectodermal and other features, led to the first report of homozygous loss-of-function variants in *PPP1R13L* in humans. This gene encodes iASPP (inhibitor of apoptosis-stimulating protein of p53), which has a role in desmosome regulation as well as in apoptosis and inflammatory pathways.

We report homozygous or compound heterozygous variants in *PPP1R13L,* also identified by ES/GS performed for severe DCM, in seven additional children from five unrelated families. This case series, and observations from orthologous animal models, provide more robust evidence that *PPP1R13L* is an important cause of recessively inherited paediatric DCM.

Key words: Paediatric dilated cardiomyopathy; *PPP1R13L*; cardiocutaneous syndrome

(180 words; word limit =200)

POSTER ABSTRACTS

1. "Genetic post-mortem in drug users with sudden cardiac death"

Dr Hannah Massey[1], Dr Leighanne Deboys[1], Dawn O'Sullivan[1] and Dr John Dean[1,2]

1. Aberdeen Royal Infirmary
2. Main contact (john.dean@nhs.net)

Key words: Sudden cardiovascular death, post-mortem, toxicology, genetic diagnosis.

Aim: To quantify our ability to make a genetic diagnosis in drug users with sudden cardiac death
(SCD).

Background: While there are European recommendations for genetic testing in SCD[1], these guidelines do not extend to drug users with positive toxicology at post-mortem. We wanted to gain a better understanding of the genetic pick up rate in this population.

Method: We undertook a 10-year retrospective study looking at genetic diagnoses in drug related deaths discussed at the joint pathology-genetic MDT. This was compared to age and provisional aetiology matched controls.

Results: 60 drug related deaths were identified, and 40 patients underwent genetic testing. 7 variants were found of which 3 were classified as benign and 4 VUS. The most common reason for genetic testing was enlarged heart at post mortem; however the genetic pick up in this group was 0. Patients with structurally normal hearts had the most variants detected. This would coincide with the majority of variants being found in arrhythmogenic genes. Family history did not influence genetic pick up. In the control group variants in arrhythmogenic genes again predominated correlating with the highest genetic pick up in patients with normal post-mortems. However in the control group 17 variants were detected of which 3 were pathogenic.

Conclusion: Our ability to make a genetic diagnosis in drug users with SCD is low. We need to undertake a larger study to characterise those drug users with a positive genetic diagnosis so testing can be rationalised.

References:

1. Fellmann et al. European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death. European Journal of Human Genetics 24 June 2019

2. "First, do no harm": re-evaluating families with a history of long QT syndrome and hypertrophic cardiomyopathy in the Irish population."

Authors: **Jane Murphy[1], Claire Kirk[1]**, Margaret Gallagher[2], Deirdre Ward[3], Terence Prendiville[4], Joseph Galvin[2], Sally Ann Lynch[5].

[1] School of Medicine, University College Dublin, Belfield, Dublin 4, Ireland.

[2] Family Heart Screening Centre, Mater Misericordiae University Hospital, 53-54 Eccles Street, Dublin 7, Ireland.

[3] Centre for Cardiac Risk in the Young, Tallaght University Hospital, Dublin 24, Ireland.

[4] Department of Cardiology, Children's Health Ireland at Crumlin, Dublin 12, Ireland.

[5] Department of Clinical Genetics, Children's Health Ireland at Crumlin, Dublin 12, Ireland.

Abstract

Background: Genetic testing for inherited cardiac conditions such as long QT syndrome and hypertrophic cardiomyopathy has evolved rapidly with next generation sequencing. The addition of new genes to diagnostic gene panels increases the likelihood of detecting disease- causing variants, but also variants of uncertain significance (VUS).

Aim: To review next generation sequencing panel results from cardiac channelopathy and cardiomyopathy patients referred to a family heart screening clinic to determine the distribution of pathogenic variants, likely pathogenic variants and VUS.

Methods: Data was collected by reviewing molecular diagnostic reports from probands.

Results: We reviewed 146 panels performed on 146 probands. There were 99 variants detected in 77 probands; 61 carried a single variant, 16 probands carried more than variant. A maximum of four variants were detected in two individuals. From 99 variants, 19 were pathogenic, 23 were likely pathogenic and 57 were VUS.

Conclusions: The diagnostic yield of variants from this cohort was 53%, with VUS accounting for 58% of the total yield. In the next phase of this study we will review the likely pathogenic variants and VUS using ACMG guidelines

Keywords: inherited cardiac conditions, gene panels, variant interpretation, ACMG guidelines, variants of uncertain significance.

3. **Elastin gene splice site variant associated arteriopathy. How harmful is it?**

Kissopoulou A[1], Gunnarsson C[2], Clausen H [3]

1. *Department of Internal Medicine and Cardiology County Council of Jönköping and Department of Medical and Health Sciences, Faculty of Health Sciences, Linköping University, Linköping, Sweden.*

2. *Department of Clinical Genetics, Department of Clinical Experimental Medicine, Linköping University, Linköping, Sweden and Centre for Rare Diseases in South East Region of Sweden, Linköping University, Linköping, Sweden.*

3. *Department of Pediatrics, Linköping University, County Council of Jönköping and Department of Clinical Sciences Lund, Lund University Skane University Hospital, Pediatric Cardiology, Lund, Sweden*

Corresponding author: Dr A.Kissopoulou, antheia.kissopoulou@rjl.se, tel: +46760343483

Disruptions of the elastin gene (ELN) are associated with supravalvar aortic stenosis (SVAS) presenting as an autosomal dominant trait or as part of the phenotype of Williams syndrome. Clinical and echocardiographic findings in patients with *ELN* mutations vary widely, even within the same family.

Here, we report a case of three siblings without any dysmorphic features, affected by different ranges of severity of SVAS. Their mother had undergone surgical repair of SVAS with pericardial patch. Her 9-year-old daughter was born with a mild pulmonary left artery branch stenosis that decreased in severity over time. Her 2-year-old son hade undergone surgical correction of severe SVAS. A microarray analysis was performed excluding Williams syndrome. Sanger sequencing though, revealed a heterozygous splice site variant in the ELN gene, NC_000007.13(NM_000501.3(ELN)):C.82+2T>G, considered pathogenic. The mother and her daughter also carry this ELN variant, hence it segregates with the phenotype. A third child with SVAS diagnosed at birth, died suddenly when he was 6 weeks old. Autopsy showed an enlarged heart with signs of acute myocardial ischemia and severely thickened and dysplastic media of the ascending aorta with disorganized elastin fibers. Genetic analysis revealed that in addition to the elastin variant he also had a vinculin VCL variant c.889C>T, that is likely pathogenic and reported to be associated with cardiomyopathy. This VCL variant is also detected in the father who does not have any heart problems.

With this case we outline the broad phenotypic spectrum of the phenotype within a single SVAS family. Splice cite mutations of the elastin gene cause SVAS with great intrafamiliar variability and even other genetic factors such as the VCL variant might be involved in the more severe expression of the phenotype.

KEYWORDS: supravalvar aortic stenosis, elastin gene

4. Heart failure, severe arrhythmia and sudden cardiac death in Marfan syndrome and related heritable thoracic aortic diseases

Anthony Demolder[1], Laura Muiño Mosquera[1,2], Laurence Campens[3], Julie De Backer[1,3]

[1]Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium.

[2]Department of Pediatrics, Division of Pediatric Cardiology, Ghent University Hospital, Ghent, Belgium.

[3]Department of Cardiology, Ghent University Hospital, Ghent, Belgium.

Contact person: Anthony Demolder

Email: anthony.demolder@ugent.be

Tel: 0032 472 08 51 01

Brief summary:

Background: Marfan syndrome (MFS) and related heritable thoracic aortic diseases (HTAD) are well- known for their aortic complications. Heart failure, severe arrhythmia and sudden cardiac death are less known in this setting but have been reported.

Methods: To define the prevalence of severe arrhythmia, heart failure and sudden cardiac death, we conducted a retrospective, single-center study of adults and children with MFS and related HTAD. The primary composite endpoint was defined as heart failure (HF), heart transplantation (HTx), severe arrhythmia (SA) or sudden cardiac death most likely due to arrhythmia (SCD). The secondary endpoint was death due to any cause.

Results: Overall, 154 patients with MFS and 32 patients with related HTAD underwent regular follow- up between 2004 and 2019. During follow-up, 8 patients reached the primary composite endpoint (3 SCD, 2 SA, 1 HF and 2 HTx). Of these 8 patients, 7 had MFS and 1 had a related HTAD (SMAD3 pathogenic variant). In total, 11 patients died during follow-up (10 MFS and 1 related HTAD). Cardiovascular causes of death in MFS were aortic dissection (3/10), SCD (2/10), SA (1/10) and HF
(1/10). Other causes of death were cancer (1/10) and unknown (2/10). The only deceased patient in the related HTAD group died due to SCD.

Conclusion: Heart failure, severe arrhythmias and sudden cardiac death are rare in patients with MFS and related HTAD. Despite their infrequency, they constitute a relevant cause of death.

Key words: Marfan, HTAD, heart failure, arrhythmia, SCD

Background:

Marfan syndrome and related heritable thoracic aortic diseases (HTAD) are well-known for their aortic complications resulting in prophylactic aortic surgery, aortic dissection and death. Life expectancy has improved due to careful follow-up and prophylactic treatment. Heart failure and arrhythmia are less known in this setting but have been reported, also as significant causes of death in these patients.

Purpose

To define the prevalence of severe arrhythmia, heart failure and sudden cardiac death in patients with Marfan syndrome and related HTAD managed according to standard recommendations.

Methods

We conducted a retrospective, single-center study of adults and children with Marfan syndrome (MFS) and related heritable thoracic aortic diseases (HTAD). Patients with confirmed pathogenic variants in the causative genes *FBN1, TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD3* and *ACTA2* underwent regular clinical follow-up with electrocardiography, echocardiography and cardiovascular MRI. The primary composite endpoint was defined as heart failure (HF), heart transplantation (HTx), severe arrhythmia (SA) or sudden cardiac death most likely due to arrhythmia (SCD). The secondary endpoint was death due to any cause.

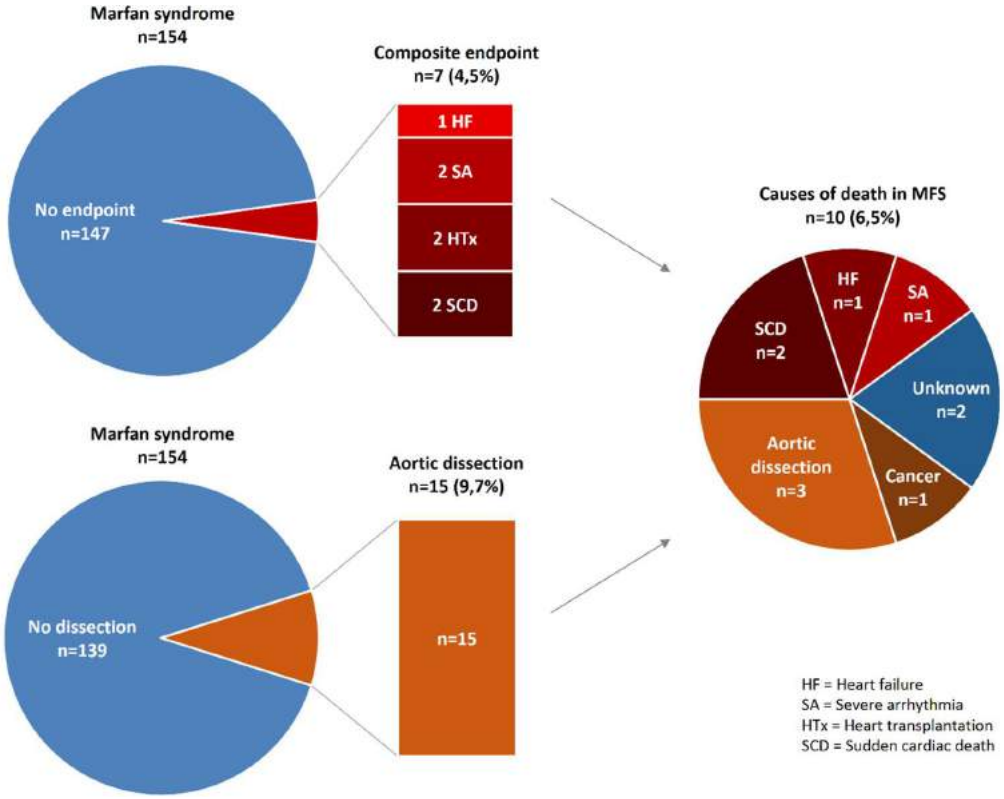
Results

Overall, 154 patients with Marfan syndrome (aged 35 [23-49] years, 51% women) and 32 patients with related HTAD (aged 41 [25-57] years, 50% women) underwent regular follow-up between 2004 and 2019. Aortic involvement (Z-score ≥2) was observed in 129 patients (83,7%) in the MFS group and 21 patients (65,6%) in the HTAD group. During follow-up, 8 patients (aged 30 [19-50], 38% women) reached the primary composite endpoint (3 SCD, 2 SA, 1 HF and 2 HTx). Of these 8 patients, 7 had MFS and 1 had a related HTAD (SMAD3 pathogenic variant). In total, 11 patients died during follow-up (10 MFS and 1 related HTAD). Cardiovascular causes of death in MFS were aortic dissection (3/10), SCD (2/10), SA (1/10) and HF (1/10). Other causes of death were cancer (1/10) and unknown (2/10). The only deceased patient in the related HTAD group died due to SCD.

Conclusion

Heart failure, severe arrhythmias and sudden cardiac death are rare in patients with MFS and related HTAD managed according to the standard recommendations. Despite their infrequency, they constitute a relevant cause of death. To identify predisposing factors associated with these rare, yet severe cardiac complications, a multicenter joint initiative is needed.

Figure 1: Heart failure, severe arrhythmia and sudden cardiac death observed in MFS



5. **Loss-of-function variants in myocardin cause congenital megabladder in humans and mice**

Arjan C. Houweling[1,19*], Glenda M. Beaman[2,3,19], Alex V. Postma[4,5,19], T. Blair Gainous[6], Klaske D. Lichtenbelt[7], Francesco Brancati[8,9], Filipa M. Lopes[10], Ingeborg van der Made[11], Abeltje M. Polstra[1,12], Michael L. Robinson[13], Kevin D. Wright[13], Jamie M. Ellingford[2,3], Ashley R. Jackson[14], Eline Overwater[1,5], Rita Genesio[15], Silvio Romano[9], Letizia Camerota[16], Emanuela D'Angelo[17], Elizabeth J. Meijers-Heijboer[1], Vincent M. Christoffels[4], Kirk M. McHugh[14], Brian L. Black[6], William G. Newman[2,3,20], Adrian S. Woolf[10,18,20], Esther E. Creemers[11,20*]

[1]Department of Clinical Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

[2]Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology Medicine and Health, University of Manchester, UK.

[3]Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

[4]Department of Medical Biology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Academic Medical Center, the Netherlands

[5]Department of Clinical Genetics, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Academic Medical Center, the Netherlands.

[6]Cardiovascular Research Institute, University of California, San Francisco, CA, USA

[7]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

[8]Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata, IDI-IRCCS, Rome, Italy

[9]Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy.

[10]Division of Cell Matrix Biology and Regenerative Medicine, School of Biological Sciences, Faculty of Biology Medicine and Health, University of Manchester, UK.

[11]Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Academic Medical Center, Amsterdam, the Netherlands.

[12]Laboratory Genetic Metabolic Diseases, Departments of Clinical Chemistry and Clinical Genetics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

[13]Department of Biology, Miami University, Oxford, Ohio, USA

[14]Center for Clinical and Translational Research, The Research Institute, Nationwide Children's Hospital, Columbus, Ohio, USA.

[15]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy

[16]Medical Genetics Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

[17]Pathology Division, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

[18]Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

[19]These authors contributed equally

[20]These authors jointly supervised this work

*Corresponce: a.houweling@vumc.nl or e.e.creemers@amc.uva.nl

Abstract

Myocardin (MYOCD) is the founding member of a class of transcriptional co-activators that bind serum response factor to activate gene expression programs coding for contractile and other cytoskeletal proteins critical in smooth- and cardiac muscle development. Insights into the molecular functions of MYOCD have been obtained from cell culture studies and, to date, our *in vivo* knowledge about MYOCD comes exclusively from experimental animals. For example, expression of dominant negative *Myocd* disrupts myocardial differentiation in embryonic frogs, while *Myocd* null mice die midgestation with failed vascular smooth muscle (SM) cell differentiation. Here, we define a devastating and often lethal human congenital disease associated with inheritance of pathogenic *MYOCD* variants, with 14 affected

individuals in four families. This disease manifests as a massively dilated urinary bladder, or megabladder, with a disrupted SM wall. These human results are supported by evidence of megabladder in two distinct mouse models with reduced *Myocd* levels. Together, these findings highlight a vital role for MYOCD in mammalian organogenesis. In conclusion, we demonstrate for the first time that variations in MYOCD result in human disease, and propose that loss-of-function variants in MYOCD cause semi-dominant congenital megabladder. This has important implications for genetic counseling of families with congenital megabladder, sheds new light on bladder development, and expands the pathophysiological spectrum of inherited SM disorders.

6. The Egyptian Collaborative Cardiac Genomics (ECCO-GEN): Defining a Healthy Volunteer Cohort

Keywords: 100 Egyptian genomes, cardiovascular disease, Africa

Yasmine Aguib[1,2*] , Mona Allouba[1,2,3*], Alaa Afify[1*], Sarah Halawa[1,4], Mohamed ElKhateb[1], Marina Sous[1], Aya Galal[1], Eslam Abdelrahman[1], Nairouz Shehata[1], Amr El Sawy[1], Mohamed Maghawry[1], Shehab Anwer[1], Omnia Kamel[1], Wessam El-Mozy[1], Hadir Khedr[1], Ahmed Kharabish[1], Nagwa Thabet[1], Pantazis Theotokis[2,3], Rachel Buchan[2,3], Risha Govind[2,3], Nicola Whiffin[2,3,8], Roddy Walsh[2,3,7], Heba Aguib[1], Ahmed Elguindy[1,2], Stuart A Cook[2,3,5,6] , Paul J Barton[2,3], James Ware[2,3,8], Magdi Yacoub[1,2,9].

**authors contributed equally*

[1] Aswan Heart Centre, Aswan, Egypt

[2] National Heart and Lung Institute, Imperial College London, London, UK

[3] Cardiovascular Research Centre, Royal Brompton Hospital and Harefield NHS Foundation Trust, London, UK

[4] The American University in Cairo, AUC Ave, Cairo, Egypt

[5] National Heart Centre Singapore, Singapore, Singapore

[6] Duke-National University of Singapore, Singapore, Singapore

[7] Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Amsterdam, Netherlands

[8] MRC London Institute of Medical Sciences, Imperial College London, London, UK

[9] Harefield Heart Science Centre, Harefield, Middlesex, United Kingdom

Abstract

Introduction: Integration of comprehensive genomic and phenotypic data from diverse ethnic populations offers unprecedented opportunities towards advancements in precision medicine and novel diagnostic technologies. Current reference genomic databases, such the Genome Aggregation Database (gnomAD), lack genetic data from the North African population. To ameliorate this knowledge gap, the Egyptian Collaborative Cardiac Genomics (ECCO-GEN) Project launched a study comprising 1000 individuals free of cardiovascular disease (CVD).

Aim: To define the genetic landscape of the understudied Egyptian population to support future studies in CVD and population genetics.

Methods: Egyptian healthy volunteers (EHVols) were recruited to Aswan Heart Centre for clinical- and genetic testing using a targeted sequencing panel of 174 genes associated with inherited cardiac conditions. Variants were interpreted in accordance with the ACMG guidelines.

Results: We present the first 391 EHVols recruited to establish a pilot phenotyped control cohort. We identified 1,262 variants in 27 cardiomyopathy genes of which 15.1% were not captured in current global (gnomAD) and regional (GME) genetic reference databases.

Conclusions: This study provides preliminary insights into genetic variation of the multi-ethnic Egyptian population. Expanding the ECCO-GEN project and integrating ancestry-specific genetic and phenotypic data will deepen our understanding of African diversity, which is crucial for precision medicine.

7. Discovery of a novel putative pathogenic truncating variant in MYH7 in Egyptian HCM patients

Mona Allouba[1,2*], Yasmine Aguib[1,2*], Alaa Afify[1], Aya Galal[1], Roddy Walsh[2,5], Pantazis Theotokis[2], Nicola Whiffin[2], Sarah Halawa[1,3], Ahmed Elguindy[1,2], Shehab Anwer[1], Stuart A Cook[2,4], Paul J Barton[2], James Ware[2], Magdi Yacoub[1,2,6]

*authors contributed equally

[1]Aswan Heart Centre, Egypt; [2]NHLI, Imperial College London, London, UK; [3]The American University in Cairo, Egypt; [4]National Heart Centre Singapore, Singapore; [5]Department of Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam UMC, Netherlands; [6]Harefield Heart Science Centre, UK

Abstract

Introduction: Hypertrophic Cardiomyopathy (HCM) is an inherited disease characterised by genetic and phenotypic heterogeneity. The genetic determinants of HCM in Egypt have not been studied, particularly in relation to controls.

Aim: To define the genetic architecture of Egyptian HCM (AhcHCM) patients and elucidate disease mechanisms of novel putative pathogenic variants.

Methods: Prospective AhcHCM patients (n=516) and Egyptian Healthy Volunteers (EHVols) (n=400) were recruited to Aswan Heart Centre for clinical phenotyping and genetic testing. Samples were sequenced for 174 genes implicated in inherited cardiac conditions (Illumina).

The excess of rare variation (gnomAD filtering allele frequency <= $4x10^{-4}$) in each HCM gene in the AhcHCM cohort over EHVols was calculated.

Results and Conclusions: A significant burden of a novel truncating variant in MYH7 (MYH7tv) was observed in the AhcHCM cohort over EHVols ($p <= 0.002$). To elucidate the underlying mechanism of MYH7tv we are using functional genomics approaches to characterise induced pluripotent stem cell-derived cardiomyocytes generated from patients' myocardial tissues harbouring the variant. In contrast to current knowledge, we hypothesize that the mutant MYH7 transcript escaped nonsense mediated decay to act as a disease-causing protein. Characterisation of the novel MYH7tv may provide deeper mechanistic insights and contribute to precision in HCM clinical practice.

Keywords: Cardiovascular Disease, Novel variant, Precision Medicine

8. Biallelic *PPP1R13L*-associated paediatric dilated cardiomyopathy: expanding the phenotypic spectrum

C.L. Turner[1], H.K. Robinson[2], L. Mallin[2], C. Armstrong[3], D. Mabin[4], E. Zaklyazminskaya[5], I. Povolotskaya[6], Y. Surikova[7], P.J. Benke[8,9], M.R. Chrisant[9], C.C. Marboe[10], M Mcdonald[11], K. Agre[12], D. Deyle[12], K M. Balashova[6], V. Kaimonov[6], N. Shirokova[6], E. Pomerantseva[6], K. McWalter[13], G. Douglas[13], S. Ellard[2,14]

(1) Peninsula Clinical Genetics Service, Department of Clinical Genetics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

(2) Molecular Genetics Department, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

(3) Paediatric Cardiac Service, Bristol Royal Hospital for Children, Bristol, UK

(4) Department of Paediatrics, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK Centre of

(5) Centre of Syncope and Cardiac Arrhythmias in Children and Adolescents, Moscow, Russia

(6) Genetics and Reproductive Medicine “Genetico”, Moscow, Russia

(7) B.V. Petrovsky Russian Scientific Center of Surgery, Moscow, Russia

(8) Charles E. Schmidt College of Medicine, Florida Atlantic University, Florida, USA

(9) Joe DiMaggio Children’s Hospital, Hollywood, Florida, USA

(10) Department of Pathology and Cell Biology, Columbia University Medical Centre, New York, USA

(11) Division of Medical Genetics, Department of Pediatrics, Duke University, Durham, NC, USA

(12) Mayo Clinic, Department of Clinical Genomics, Rochester, Minnesota, USA

(13) GeneDx Inc., Gaithersburg, Maryland, USA

(14) Institute of Biomedical and Clinical Science, College of Medicine and Health, Exeter, UK

claire.turner12@nhs.net 01392 405749

Paediatric dilated cardiomyopathy (DCM) has a reported annual incidence of 0.57 cases per 100,000. Although rare, it is associated with significant morbidity and mortality, being a common reason for heart transplantation and sudden death. It is multifactorial but a proportion of cases have a genetic aetiology with significant heterogeneity. Genomics England PanelApp currently includes around 50 causative genes, but exome (ES) or genome sequencing (GS) is important for detecting emergent genetic causes.

ES, utilised recently to investigate a single consanguineous family in which five children had DCM and variable ectodermal and other features, led to the first report of homozygous loss-of-function variants in *PPP1R13L* in humans. This gene encodes iASPP (inhibitor of apoptosis-stimulating protein of p53), which has a role in desmosome regulation as well as in apoptosis and inflammatory pathways.

We report homozygous or compound heterozygous variants in *PPP1R13L,* also identified by ES/GS performed for severe DCM, in seven additional children from five unrelated families. This case series, and observations from orthologous animal models, provide more robust evidence that *PPP1R13L* is an important cause of recessively inherited paediatric DCM.

Key words: Paediatric dilated cardiomyopathy; *PPP1R13L*; cardiocutaneous syndrome

9. A truncating *KCNQ1* variant causing Jervell and Lange-Nielsen syndrome, but not Long QT syndrome

Dr. James Cranley (presenting), Cardiology Registrar, Norfolk and Norwich University Hospital, Norwich, UK Email james.cranley@nhs.net; Phone +44 7739 914 901

Dr. Greg Mellor, Consultant Electrophysiologist, Royal Papworth Hospital, Cambridge, UK
Email gregmellor@nhs.net; Phone +44 7967 713 345

Keywords- Jervell and Lange-Nielsen Syndrome; KCNQ1; Genomic Medicine; Mechanisms of disease

Jervell and Lange-Nielsen syndrome (JLNS) is a rare condition comprising deafness and QT prolongation. Pathogenic loss-of-function variants in the potassium channel gene *KCNQ1* cause Long QT Syndrome 1 (LQT1) or, when biallelic, JLNS1.
A 3 month old girl was found to have profound sensorineural hearing loss. Her ECG revealed gross QT prolongation (QTc 620ms). Genetic sequencing showed that she was homozygous for a highly deleterious nonsense mutation in *KCNQ1*, c.433delA (p.Tyr148LeuFS*89).
The proband's parents and sibling were found to be carriers of the same variant but had normal resting ECGs and exercise treadmill tests.
We report the first case of JLNS1 due to biallelic c.443delA variants in *KCNQ1.* Notably, our case illustrates that heterozygote carriers of this mutation exhibit normal repolarisation.

We discuss the mechanism by which mutations in the same gene may cause both dominant (LQT1) and recessive (JLNS1) disease patterns. In particular, highly deleterious mutations result in gene products incapable of coassembly into the tetramer Kv7.1 channel, leading to channels comprised of wild-type subunits with a normal phenotype when in the heterozygote state (JLNS1). This contrasts with less deleterious mutations producing subunits which are incorporated into channels causing, paradoxically, an abnormal phenotype even with one aberrant copy (LQT1).

10. A rapidly growing cardiac fibroma in Gorlin syndrome

Rosalyn Jewell (1), Michael Blackburn (2), Osama Jaber (3), Helen Jepps (4) and Dominic Hares (2)

1. Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust
2. Congenital Cardiac Service, Leeds Teaching Hospitals NHS Trust
3. Cardiac Surgery Services, Leeds Teaching Hospitals NHS Trust
4. Department of Paediatrics, Bradford Teaching Hospitals NHS Trust

Rosalyn.jewell@nhs.net 07816773519

Key words: Gorlin syndrome, cardiac fibroma

Cardiac fibromas in Gorlin syndrome are typically benign and most cause no symptoms. Conservative treatment is usually recommended if there is no obstruction or arrhythmias. We report a case of a child born with a 3.3cm diameter mass arising from the septum, with features suggestive of a cardiac fibroma. Genetic testing identified a likely pathogenic PTCH1 variant, and the child had macrocephaly, consistent with Gorlin syndrome. Subsequently the child's father was also found to have the condition.

The ventricular mass started to grow rapidly. At four months of age, it was 4.6 cm in size, with vacuolisation evident on scans. The mass was severely displacing the left coronary artery and causing near total obstruction to the left pulmonary artery and main bronchus. There was no cardiac obstruction or rhythm disturbance.

In view of this unusual behaviour, the mass was biopsied and confirmed as being a fibroma. A sub-total resection took place, but the residual fibroma did not continue to grow. The patient has remained well post-operatively and is thriving.
Rapidly growing cardiac fibromas are rare, but this case demonstrates this can be a characteristic of fibromas associated with Gorlin syndrome.

11. A rare form of early onset dilated cardiomyopathy: congenital disorder of glycosylation – DOLK (CDG-DOLK). A case presentation and literature review.

Gable M[1]; Whittington R[1]; Low K[2]; Armstrong C[3]; Grünewald S[4]; Moore R[1]; Williams M[1].

Contact email: Mary.Gable@nbt.nhs.uk; Contact telephone: 0117 414 6164.

1. Bristol Genetics Laboratory/South West Genomics Laboratory Hub, Southmead Hospital,Bristol BS10 5NB. 2. Bristol Regional Genetics Service, St Michael's Hospital, Bristol, BS2 8EG. 3. Bristol Heart Institute, Bristol Royal Infirmary, Bristol, BS2 8HW. 4. Great Ormond Street Hospital, UCL Institute of Child Health, University College London, London, WC1E 6BT.

Key words: paediatric cardiomyopathy; dilated cardiomyopathy; *DOLK* gene; congenital disorder of glycosylation.

Paediatric cardiomyopathy has a complex heterogeneous aetiology, and it is vital that rare autosomal recessive genes with associated cardiomyopathy as a key or presenting feature are included in gene panels within the Genomic Medicine Service.

We present a case study of a 15-year female with premature ovarian failure, psoriasis, femoral artery thrombosis and severe biventricular cardiomyopathy following a viral illness, which rapidly progressed to multi-organ failure and death.

Analysis on the Bristol 120 gene cardiomyopathy panel revealed that this patient was compound heterozygous for two likely pathogenic variants in the *DOLK* gene: c.358G>A, p.(Ala120Pro) and c.1224_1225del, p.(Ile409Leufs*22). This was confirmed by biochemical analysis of transferrin glycoforms, and parental segregation testing. Variants in *DOLK*, encoding the dolichol kinase enzyme, are associated with the very rare congenital disorder of glycosylation CDG-DOLK, a type I CDG.

Around 20 cases of CDG-DOLK across 9 families are reported in the literature to date, all but two patients developed dilated cardiomyopathy, and there is a marked variability in clinical features and age of onset, ranging from neonate to teenage[1-5]. We present this clinical case in the context of a review of CDG-DOLK published families.

References:

1. Kranz *et al* (2007) Am J Hum Genet 80:433.
2. Lefeber *et al* (2011) PLoS Genet 7(12):e1002427.
3. Helander *et al* (2013) Mol Genet Metab 110:342.
4. Lieu *et al* (2013) Mol Genet Metab 110(4):484.
5. Rush *et al* (2017) Am J Med Genet 173A:2428.

12. Challenge of variant classification : The example of hypertrophic cardiomyopathy

S. Fokstuen[1], Ch. Gruner[2], H. Hammer[2], M. Guipponi[1], E. Hammar[1], M. Beghetti[3], Ph. Meyer[4], M. Abramowicz[1], J.-L. Blouin[1]

[1]*Service of Genetic Medicine, University Hospitals of Geneva, Geneva, Switzerland*
[2]*Department of Cardiology, Herzzentrum University Hospital Zürich, Zürich, Switzerland*
[3]*Pediatric Cardiology, University Hospitals of Geneva, Geneva, Switzerland*
[4]*Cardiology, University Hospitals of Geneva, Geneva, Switzerland*

High throughput sequencing technology has made it possible to analyze all known hypertrophic cardiomyopathy (HCM) genes in parallel. As a result variants of unknown clinical significance (VUS) are increasingly detected. The situation is aggravated by the fact that apart from the well known described main HCM genes, most diagnostic laboratories perform large panel analysis including genes of other cardiomyopathy subtypes and/or genes whose evidence is only limited. At the University Hospitals of Geneva we currently analyze by targeted exome sequencing 65 genes responsible for all types of cardiomyopathies. We present here the results of 55 unrelated HCM probands. At least one pathogenic or likely pathogenic variant was found in 48 % (26/54). *MYBPC3* gene variants accounted for 77 % (20/26). The other 6 variants were found in *MYH7* (N=2), *TPM1* (n=1), *MYPN* (n=1), *TNNI3* (n=1), and *TNNT2* (n=1). Six of the 26 probands had in addition a second variant of unknown clinical significance. In 22 % (12/54) only a VUS was identified and in 29 % (16/54) no variant of clinical significance was found. The ACMG guidelines for variant classification are challenging for patients with HCM, especially due to the incomplete penetrance as clinically asymptomatic persons may carry VUS.

13. **The role of Genetic Counsellors in UK Inherited Cardiac Conditions Clinics: past, present and future**

Heidy Brandon & Ginny Attard, Registered Genetic Counsellors, South West Thames Regional Genetics Service, St George's Hospitals NHS Foundation Trust, London, UK

Contact: heidy.brandon@nhs.net or 020 8275 2038

Keywords: Genetic Counsellors, Genomic Counselling, Communication, Professional Practice

The role of genetic counsellors in UK Inherited Cardiac Conditions (ICC) clinics has evolved since the early 2000s. Initially, Cardiologists were offering genetic testing on a research basis. Nurses up-skilled in genetics to become genetic counsellors and were embedded in regional genetics services. Genetic testing was based on single genes at the time. We have now evolved to have genetic counsellors working out of both regional genetics services and solely in ICC clinics offering genetic panel testing. The introduction of panel testing has increased the number of variants being identified and genetic counsellors also have a role in the interpretation process. In the future, genetic and the newly trained genomic counsellors' role will change with the introduction and support of mainstream testing and eventually genomic testing. We will propose a new model for UK genetic/genomic counsellors working collaboratively with our colleagues in inherited cardiac clinics in the future based on our clinical experience. There will be an emphasis on the utilisation of our skills in communicating complex information in a manner approachable for patients, as well as counselling, variant interpretation and education.

14. The yield from genetic testing for Long QT (LQT) syndrome in Sudden Arrhythmic Death (SADS) families in The Cardiac Risk for younger Persons (CRY) Centre in Tallaght University Hospital Ireland

H. Connaughton, L Doorley, C. Barry, R. Kinsella, A. Green, D. Ward

Background: The first genes associated with LQT syndrome were first discovered between 1995 and 1996. The following 10 years involved the discovery of novel mutations and therefore paved the way for the development of risk stratification based on QTC duration and the genetic substrate.

Purpose: The aim of this study was to assess the proportion of patients referred for genetic testing for Long QT (LQT) Syndrome in SADS families in whom clinically useful results are obtained.

Method: A retrospective analysis was performed on the clinical records of all patients assessed at the centre. Patients were referred for genetics as appropriate, based on family history and the results of non-invasive cardiac investigations including Electrocardiogram (ECG), Echocardiograph (ECHO), Exercise Stress testing (EST) and 24 hour Holter monitoring.

Results:
366 individuals were referred for LQT genetics from a total of 174 families. Of these individuals 234 of them were sent due to a family history of SADS +/- an abnormal clinical finding. A total of 41% of these individuals were index cases and a positive result was found in 17%.
Of the 59% that were sent for predictive LQT genetics 39% of them were positive for LQT with a further 19% awaiting results to date.

Conclusion: Genetic testing is a very important tool in evaluating inherited cardiac conditions. Referral to genetics is not for diagnosis, but to allow accurate predictive testing in the family

Dr Deirdre Ward – Consultant Cardiolgist, Helen Connaughton Clinical Nurse Specialist (CNS), Ciara Barry – CNS, Rita Kinsella CNS, Laura Doorley CNS

Hospital - Tallaght University Hospital, Dublin 24 , Ireland

Dr Deirdre Ward – Deirdre.ward@tuh.ie;

Helen Connaughton – helen.connaughton@tuh.ie

Phone Number - 00353 1 4143058

15. Copy number variants in inherited cardiomyopathy genes: findings from a large cardiomyopathy cohort.

Helen Sage, Jesse Hayesmoore, Teresa Lamb, Louise Williams, Anthony O'Rourke, Karen McGuire, Edward Blair, Hugh Watkins, Kate Thomson.

Introduction: The vast majority of pathogenic variants in inherited cardiomyopathy (CM) genes involve one, or a small number, of nucleotides. Larger copy number variants (CNVs), encompassing all or part of a gene, have been described; however, accurate estimates of the frequency of this class of variant are not available. We report the outcomes of CNV analyses of cardiomyopathy genes in a large patient cohort.

Methods: CNV analyses were undertaken using dosage quotient analysis of massively parallel sequencing data and/or MLPA on 3839 individuals referred for genetic testing for hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), or arrhythmogenic right ventricular cardiomyopathy (ARVC). Variants were confirmed by MLPA or long-range PCR. Investigations were undertaken to explore variant pathogenicity.

Results: 35 CNVs were detected in 15 genes (*ACTN2*, *DMD*, *DSC2*, *DSG2, DSP, FLNC*, *GLA*, *LMNA*, *MYBPC3*, *MYH7*, *PKP2*, *PLN, TNNI3*, *TTN*, *VCL*), in 51/3839 probands (1.3%). The majority were detected in two genes: *MYBPC3* and *PKP2*. 19/35 CNVs were classified as pathogenic or likely pathogenic.

Conclusions: Pathogenic CNVs were detected in ~1% of our CM cohort; the majority in genes where haploinsufficiency is a known disease mechanism. These findings highlight the importance of CNV analyses in cardiomyopathy genes.

16. Unheralded VF arrest in a teenager carrying a rare RYR2 gene variant: CPVT diagnosis made?

M Ilina[1], R Myles[2], D Oxnard[3], R McGowan[3]

Department of Paediatric Cardiology, Royal Hospital for Children, Glasgow

Department of Cardiology, Glasgow Royal Infirmary

Department of Clinical Genetics, Queen Elizabeth University Hospital, Glasgow

Authors contacts: m.ilina@nhs.net; ruthmcgowan@nhs.net

Key words: Sudden death, CPVT, RYR2

A 15-year-old previously well female with no family history of sudden death, complaining of flu-like symptoms, was resuscitated after a cardiac arrest at home. Investigations included laboratory myocarditis screen, exercise ECG, Echocardiography, CMR and arrhythmia gene panel. Positive Coronavirus PCR, lateral repolarisation abnormalities, no exercise-induced arrhythmia on beta- blocker, impaired but recovering ventricular function and raised hsTroponin I levels pointed to myocarditis as a possible cause. Owing to lack of diagnostic certainty, the family opted for an S-ICD implant. Follow up exercise ECG on a day when beta-blocker was accidentally omitted, provoked bidirectional ventricular couplets. Arrhythmia gene panel yielded a rare RYR2 gene variant (c.11876C>T, p.Ser3959Leu). Several years prior to this event, both parents in their 40's had cardiac investigations: mother (adopted) complained of palpitations, a run of non-sustained monomorphic VT on ambulatory ECG was not reproduced on exercise, CMR was normal. Father was investigated for chest pain and had ventricular couplets brought on by exercise. Both were now tested: father carries the same RYR2 gene variant. Our case report is the second sudden (aborted) cardiac death in association with this RYR2 gene variant in the literature and highlights the importance of testing for arrhythmia genes in similar presentations.

17. Whole genome and transcriptome sequencing of post-mortem cardiac tissues from sudden cardiac death victims identifies a gene regulatory variant in *NEXN*

S. B. Jacobsen[1*], J. D. Andersen[1], L. C. Trudsø[1], M-L. Kampmann[1], J. Banner[2], N. Morling[1]

[1] *Section of Forensic Genetics, Department of Forensic Medicine, Faculty of Health and Medical Sciences, University of Copenhagen*

[2] *Section of Forensic Pathology, Department of Forensic Medicine, Faculty of Health and Medical Sciences, University of Copenhagen;* *E-mail address: stine.b.jacobsen@sund.ku.dk TEL: +45 35326916

Sudden cardiac death (SCD) is a devastating event that constitutes a diagnostic challenge in forensic pathology, especially in cases with structurally normal hearts. Due to the high heritability of diseases underlying SCD, post-mortem genetic analyses, so-called molecular autopsies, have been an expanding field of research in recent years. The vast majority of studies have focused on genetic variation in coding regions of cardiac genes, resulting in the identification of pathogenic variants in up to 30% of SCD cases. However, much remain unknown about potential associations between SCD and variants in non-coding regions of the genome.
In this study, we performed whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) to explore the potential association between genetic variants in non-coding regulatory regions and gene expression levels. WGS was performed using frozen tissue and WTS using formalin-fixed, paraffin-embedded (FFPE) cardiac tissue from nine sudden arrhythmic death syndrome (SADS) and three sudden unexplained death in infancy (SUDI) deceased individuals.
We identified a variant in the promoter region of the gene *NEXN*, c.-194A>G, that was found to be statistically significantly ($p < 0.05$) associated with an approximately 10 time decreased expression of *NEXN* and cardiac hypertrophy. This study highlights the potential of using WTS to evaluate the effect of genetic variation in non-coding regulatory regions.

Keywords: Sudden cardiac death · Molecular autopsy · Whole genome sequencing · Whole transcriptome sequencing · Formalin-fixed, paraffin-embedded tissue · NEXN

18. A novel case of Meester-Loeys syndrome is identified through the 100,000 Genomes project in an adult patient with a previous clinical diagnosis of Beals Syndrome.

Karen Low[1], Carolyn Dent[2], Alison Hills[2,3], Maggie Williams[2], Rebecca Whittington[2]

[1] University Hospitals NHS Trust, [2] North Bristol NHS Trust, [3]Wessex Regional Genetics Laboratory

We present a case of an adult male with a clinical diagnosis of Beals Syndrome in childhood. As a baby he was noted to have a unilaterally abnormal earlobe of crumpled appearance and severe bilateral talipes requiring multiple casting and operations which meant that he was "in and out of plaster until the age of 13". He was tall with significant camptodactyly and joint problems. His mother is 5'7, with congenital hammer toes requiring a number of foot operations. She also has pes planus and recurrent locking of her finger joints. There is a maternal family history of sudden death in males in adulthood.

Array CGH in the proband initially detected a maternally inherited duplication on the X chromosome which was considered unlikely to be related to his phenotype. Gene panel testing for aortopathy and distal contractures were both normal. Subsequently a hemizygous splice variant in *BGN* ,
c.351+1G>A, was detected through the 100,000 genomes project; *BGN* variants are associated with X-linked Meester-Loeys syndrome. Family studies showed this had been inherited from his mother. We review the literature of this rare condition and discuss the important genetic counselling and screening implications of this result for the family.

Contact details of presenting author:
Karen.low@uhbristol.nhs.uk
01173425917

19. INVS as a novel gene for hypoplastic left heart syndrome.

Alkorashy Maarab[1,*], Alhashem Amal[2], Takroni Saud[1,3], Alruwaili Nadia[1], Al-Hassnan Zuhair[1,3]

[1]Cardiovascular Genetics Program, King Faisal Specialist Hospital & Research Centre KFSH&RC, Riyadh, Saudi Arabia.

[2]Department of Paediatrics, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.

[3]Deptartment of Medical Genetics, KFSH&RC, Riyadh, Saudi Arabia.

*__Correspondence to:__

Maarab Alkorashy, Post doctoral fellow. Cardiovascular Genetics Program. Department of Genetics, Research Centre. MBC-03, King Faisal Specialist Hospital & Research Centre, Riyadh, KSA malqurash@kfshrc.edu.sa

Key Words:

Hypoplastic left heart syndrome, Congenital heart disease, whole exome sequencing, homozygosity mapping, left ventricle, Inversin.

Abstract

Hypoplastic left heart syndrome (HLHS), is a serious complex congenital heart disease (CHD) affecting the left ventricle (LV), aorta, and mitral valve. If is not surgically repaired, HLHS usually causes death within the first weeks of life. While the genetic basis of HLHS remains largely undetermined, mutations in several genes have been identified through whole exome sequencing (WES).

In a consanguineous family with three affected children, we performed a combined approach of homozygosity mapping and WES that identified a novel homozygous loss-of-function variant in *INVS.* Recessive mutations in INVS are known to cause infantile nephronophthisis which can be associated with heart valve and septal defects. INVS encodes a protein that contains ankyrin domains and two IQ calmodulin binding domains that have a major role in renal tubular development. Mutated *INVS* in mice causes complex heart defects and renal malformations. Our findings suggest that *INVS* is a novel candidate for HLHS and provide new paradigm for complex CHD.

20. Atypical *COL3A1* variants (glutamic acid to lysine) cause vascular Ehlers-Danlos Syndrome with a consistent phenotype of tissue fragility and skin hyperextensibility.

Neeti Ghali[1*], MD, Duncan Baker[2], FRCPath (Dip), BSc, Angela F Brady[1], PhD, Nigel Burrows[3], MD, FRCP, Elena Cervi[4], PhD, Deirdre Cilliers[5], MD, Michael Frank[6], MD, Dominique P Germain[7], MD, PhD, David JS Hulmes[8], PhD, Marie-line Jacquemont[9] , MD, Peter Kannu[10], FRACP, Henrietta Lefroy[5], MRCP, Anne Legrand[11] , PharmD, F. Michael Pope[12], MD, Lisa Robertson[13], MRCP, Anthony Vandersteen[14], PhD, Kate von Klemperer[15], MRCP, Renarta Warburton[2], BSc, MSc, Margo Whiteford[16] BSc, FRCP and Fleur van Dijk, MD, PhD[1]

[1] *Ehlers-Danlos Syndrome National Diagnostic Service London, North West Thames Regional Genetics Service, London North West Healthcare University NHS Trust, Harrow, Middlesex, UK*

[2] *Connective Tissue Disorders Service, Sheffield Diagnostic Genetics Service, Sheffield, UK*

[3] *Department of Dermatology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

[4] *Centre of Inherited Cardiovascular Diseases, Great Ormond Street Hospital NHS Foundation Trust, London, UK*

[5] *Oxford Centre for Genomic Medicine, Oxford University NHS Foundation Trust, Oxford, UK*

[6] *AP-HP Hopital European Georges Pompidou, Departement de Genetique, Sercie de Medecine Vasculaire et Centre de Reference des Maladies Vasculaires Rares, Paris, France*

[7] Division of Medical Genetics, University of Versailles, Paris-Saclay University, 78180 Montigny, France

[8] *UMR5305, CNRS / Université Claude Bernard Lyon 1, Lyon, France*

[9] Medical Genetics Unit, CHU La Réunion, Saint-Pierre, France

Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, Canada

[1] *Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Centre de Référence des Maladies Vasculaires Rares, Paris, France*

[2] *Department of Dermatology, Chelsea & Westminster Hospital NHS Foundation Trust, London, UK* [13] *Department of Clinical Genetics, Aberdeen Royal Infirmary, Scotland*

[14] *Maritime Medical Genetics Service, IWK Health Centre, Halifax, Nova Scotia, Canada*

[15] *Department of Cardiology, St Barthlomew's Hospital, London, UK*

[16] *Clinical Genetics West of Scotland Regional Genetics Service, Queen Elizabeth University Hospital Glasgow, UK*

Dr. Neeti Ghali

Name of presenter

ABSTRACT

The Ehlers-Danlos syndromes (EDS) are a group of rare inherited connective tissue disorders.

Vascular EDS (vEDS) is caused by pathogenic variants in *COL3A1*, most frequently glycine

substitutions. We describe the phenotype of the largest series of vEDS patients with glutamic acid to lysine substitutions (Glu>Lys) in *COL3A1* which were all previously considered to be variants of unknown significance.

Clinical and molecular data for seven families with three different Glu>Lys substitutions in *COL3A1* were analysed.

These Glu>Lys variants were reclassified from variants of unknown significance to either pathogenic or likely pathogenic in accordance with ACMG guidelines. All individuals with these atypical variants exhibited skin hyperextensibility as seen in individuals with Classical EDS and Classical-like EDS and evidence of tissue fragility as seen in individuals with vEDS.

The clinical data demonstrate the overlap between the different EDS subtypes and underline the importance of next-generation sequencing gene panel analysis. The three different Glu>Lys variants point towards a new variant type in *COL3A1* causative of vEDS which has consistent clinical features. This is important knowledge for *COL3A1* variant interpretation. Further follow-up data are required to establish the severity of tissue fragility complications compared to patients with other recognized molecular causes of vEDS.

KEYWORDS- Ehlers-Danlos Syndrome; *COL3A1*; Vascular EDS I consent for inclusion in the competition

21. **Hypertrophic cardiomyopathy and pregnancy outcomes**

Pooja Sikka[1], Vanita Suri[1], Neelam Aggarwal[1], Seema Chopra[1], Ajay Bahl[2]
1 Department of obstetrics and gynaecology, 2 Department of cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh.

Background:

Hypertrophic cardiomyopathy (HCM) is a complex, genetic cardiac disorder, the exact incidence of which in pregnancies is unknown. Both obstetricians and cardiologists face the difficult issue of managing HCM in pregnancy as controversies still persist regarding risks associated with pregnancy and delivery. HCM is considered a WHO class 2 and 3 risk, implying thereby that there is a moderate risk of morbidity in most women and a significant risk for few. To date, pregnancy outcome data for these patients is scarce. Though small studies have reported no deaths associated with pregnancy in HCM, some have highlighted several maternal complications. Widespread use of echocardiography and both genetic and clinical screening of families with HCM has led to a higher number of women being diagnosed as HCM nowadays. We report the experience of pregnancies with HCM in a tertiary care hospital in North India.

Aims:

To study maternal and fetal outcomes in women with hypertrophic cardiomyopathy and to identify factors that may influence pregnancy outcomes.

Methods:

This was a retrospective analysis of registry data. All patients with hypertrophic cardiomyopathy registered in the cardio-obstetric clinic as well as hypertrophic cardiomyopathy cohort in department of cardiology between January 2004 and June 2019 were included in the study. Clinical data, mode and time of delivery, antenatal, intrapartum and postpartum complications and fetal outcomes were analyzed. Severity of left ventricular hypertrophy, left ventricular outflow tract obstruction, arrhythmias were also be recorded and correlated with pregnancy outcomes. Risk factors contributing to adverse maternal and fetal outcomes were studied.

Results:

There were 16 pregnancies in 8 women (range 1-4) with HCM during the study period. Mean age was 24.75±3.51 years. Mean left ventricular wall thickness was 20±2.5 mm. Two patients became symptomatic for first time during first pregnancy and were diagnosed to have HCM whereas 6 women were known to have HCM prior to pregnancy. Two patients had left ventricular outflow tract obstruction (LVOTO) whereas on developed LVOTO only during her fourth pregnancy. One of these underwent alcohol septal ablation after the first of 3 pregnancies. Five women did not have LVOTO. Two women had restrictive physiology. Four were normal vaginal delivery, 8 had lower section caesarean section, all for fetal indication and 4 underwent medical termination of pregnancy. Increase in symptoms to NYHA class III/IV occurred in 3 pregnancies while 1 patient had aggravation of symptoms soon after caesarean section. There was no increase in symptoms in 12 pregnancies. Of the 7 pregnancies in women with LVOTO, 2 had aggravation of symptoms whereas aggravation of symptoms occurred in 2 of 9 pregnancies which did not have LVOTO. Of 2 women with restrictive physiology became symptomatic at as early as 24 weeks of gestation. Her symptoms rapidly progressed and by 26

heart failure with pulmonary oedema and pericardial effusion. She had an intrauterine fetal death at this time. She was managed with beta blockers and diuretics. Induction of labor was done with pitocin for pregnancy termination at 28 weeks. She delivered uneventfully and there was a gradual improvement in her symptoms after delivery. Another patient had intrauterine fetal death at 16 weeks of gestation. This was not associated with increase in symptoms related to HCM.

Conclusions:

Pregnancy is usually well tolerated in women with HCM, though severe symptoms occur in 25% pregnancies which improve with delivery. Most pregnancies in women with LVOTO are well tolerated. HCM patient with restrictive physiology developed heart failure with resultant adverse pregnancy outcome.

22. Genome sequencing for inherited cardiac conditions: analysis of 201 cardiovascular patients recruited through the 100,000 Genomes project by the West of England and South West NHS Genomic Medicine Centres.

Rebecca Whittington[1], Carolyn Dent[1], Hannah Robinson[2], Julie Evans[1], Mary Gable[1], Karen Low[5], Alan Donaldson[5,6], Ruth Newbury-Ecob[4,5], Claire Turner[2], Martina Muggenthaler[2]; Catherine Carpenter-Clawson[4], Aileen McCloughlin[4], Ana Juett[3], Graham Stuart[7], Sian Ellard[2,3] and Maggie Williams[1].

[1]North Bristol NHS Trust, [2]Royal Devon & Exeter NHS Foundation Trust, [3]South West NHS Genomic Medicine Centre, [4]West of England NHS Genomic Medicine Centre, [5] University Hospitals Bristol NHS Trust, [6]Gloucestershire Royal Hospital, [7] Bristol Heart Institute.

Contact email: Rebecca.whittington@nbt.nhs.uk; Contact telephone: 0117 414 6175

Key words: 100,000 genomes; inherited cardiac conditions; whole genome sequencing

The West of England and South West NHS Genomic Medicine Centres have recruited 276 cardiovascular index cases to the 100,000 Genomes Project, representing 7.4% of the total cardiac
cohort of 3728 cases. Many patients have previously undergone multiple rounds of genetic testing without a diagnosis.

Initial analysis of whole genome sequencing data is on phenotype driven (HPO) assigned gene
panels curated, through PanelApp. This identified 10 pathogenic /likely pathogenic or candidate variants. Additional analysis searching for *de novo* and biallelic recessive variants outside of applied gene panels was performed for cases with no tiered variants and identified 2 additional diagnoses.

Analysis identified a hemizygous *BGN* splice variant and *FLNC* nonsense variant; ending the diagnostic odyssey for these patients. A gene-agnostic approach adapted from an in-house trio exome pipeline, identified bi-parental variants in *PPP1R13L*, not included in the DCM panel due to limited literature evidence; additional cases demonstrating gene-disease association were identified through GeneMatcher. The importance of timely updating of gene-panels in PanelApp is highlighted by a *NOTCH1* missense variant, reported as likely pathogenic by in-house congenital heart defect panel testing, but not highlighted by the 100,000 genomes variant tiering process.

23. Major Genetic Contributors to Nonsyndromic Tetralogy of Fallot.

Dr. Richard Monaghan, PhD., Research Associate, University of Manchester. Dr. Donna Page, PhD., Lecturer, Manchester Metropolitan University.
Dr. Simon Williams, PhD., Bioinformatician, University of Manchester.
Prof. Bernard Keavney, BM, BCh, DM, FRCP, British Heart Foundation Professor of Cardiovascular Medicine and Consultant Cardiologist, Central Manchester University Hospitals NHS Trust.

Abstract-

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect. Rare genetic variants have been identified as important contributors to the risk of congenital heart disease, but relatively small numbers of TOF cases have been studied. We used whole exome sequencing to assess the prevalence of unique, deleterious variants in the largest cohort of nonsyndromic TOF patients reported to date. The presence of such variants was defined by their absence in the Genome Aggregation Database and bioinformatic prediction of their deleterious effect on function. The enrichment of variants in two genes, *NOTCH1* and *FLT4*, surpassed thresholds for exome-wide significance ($P<5\times10^{-8}$) after correction for multiple comparisons. *NOTCH1* was most frequently found to harbour unique, deleterious variants (4.5%; 95% CI, 3.2%–6.1%). Three *NOTCH1* variants were subjected to functional evaluation, and two showed a reduction in Jagged1-induced NOTCH signalling. *FLT4* variants were found in 2.4% (95% CI, 1.6%–3.8%) of our cohort. In addition, variants in the well-established TOF gene, *TBX1*, and the genes were also significantly enriched. Our study underlines the importance of sequencing large cohorts of CHD cases in order to further discover their genetic basis.
key words: congenital heart disease, exome sequencing, Tetralogy of Fallot

24. Genetic analysis of the *DMD* gene in a Dilated Cardiomyopathy Cohort.

Teresa Lamb[1*], Jesse Hayesmoore[1], Louise Williams[1], Anthony O'Rourke[1], Ed Blair[2], Hugh Watkins[3,4], Karen McGuire[1], Kate Thomson[1].

[1]Oxford Medical Genetics Laboratory, Churchill Hospital, Oxford University NHS Foundation Trust, Oxford
[2]Oxford Centre for Genomic Medicine, Nuffield Orthopaedic Centre, Oxford University NHS Foundation Trust, Oxford
[3]Radcliffe Department of Medicine, University of Oxford, Oxford
[4]Division of Cardiovascular Medicine, John Radcliffe Hospital, Oxford University NHS Foundation Trust, Oxford
[*]Corresponding author

Contact: Email - teresa.lamb@ouh.nhs.uk; Telephone - 01865225591

Abstract:

Introduction: Pathogenic variants in the *DMD* gene cause a spectrum of X-linked muscle disorders including Duchenne and Becker muscular dystrophies and *DMD*-related dilated cardiomyopathy (*DMD*-DCM). *DMD*-DCM can present (in males or females) with left ventricular dilation and congestive heart failure, with no clinical evidence of skeletal muscle disease. Confirming a diagnosis of *DMD*-related disease has implications for clinical and family management. Although considered a relatively infrequent cause of isolated DCM, data from large DCM cohorts is lacking. We report the outcomes of *DMD* analysis in our DCM cohort.

Method: *DMD* analyses were undertaken by next generation sequencing, as part of a 35+ gene panel, on 955 probands referred for DCM testing. Variants were confirmed by Sanger sequencing or MLPA, and investigations were conducted to explore variant pathogenicity.

Results: 31 *DMD* variants were investigated in 955 probands (3.2%); 5 variants were classified as pathogenic (0.5% of probands), the remainder were classified as variants of uncertain significance.

Conclusions: Pathogenic *DMD* variants were detected in ~0.5% of probands in our DCM cohort, suggesting that this is not an infrequent cause of isolated DCM. Inclusion of *DMD* on DCM gene panels is justified as it increases the diagnostic yield and clinical utility of testing.

Key words: DMD; DCM; dilated; cardiomyopathy

25. A case report of an adult male with a new diagnosis of 22q11.2 deletion syndrome discovered when asked to evaluate a genetic cause for aortic root dilatation: do we need to include 22q11.2 in the aortopathy panel?

Keywords (6)

22q11.2 deletion syndrome; aortic dilatation; adult

Thomas Wright (*Main Presenter*)*[1,2;] Alisdair McNeill[1,3]

1. Sheffield Children's NHS Foundation Trust, Sheffield Clinical Genetics Service, OPD2, Northern General Hospital, Herries Road, Sheffield, United Kingdom, S5 7AU
2. Department of Molecular Biology and Biotechnology, University of Sheffield, Firth Court, Western Bank. Sheffield, United Kingdom, S10 2TN
3. Sheffield Institute of Translational Neuroscience, University of Sheffield, 385a Glossop Road, Sheffield, United Kingdom, S10 2HQ

Corresponding author:

*Dr Thomas Wright; Email: TEBWright1@sheffield.ac.uk

Abstract

22q11.2 deletion syndrome (22q11.2DS) is the most common chromosomal microdeletion disorder, with a highly variable phenotype including a broad range of cardiac malformations and extracardiac features. The cardiac phenotype in patients with 22q11DS can be severe and are typically conotruncal defects such as tetralogy of Fallot (TOF). A small case series from 2009 reported aortic root dilatation in the absence of other attributable structural cardiac disease in children with 22q11.2DS. A cross-sectional study by the same authors report paediatric and adolescent 22q11.2DS patients with TOF and aortic arch anomalies with increased aortic annular and aortic sinus dilatation. The current management

consensus for cardiac evaluation for 22q11.2DS is an echocardiogram at diagnosis only. We report an adult case of 22q11.2DS in a 49-year-old male diagnosed following evaluation of genetic cause for aortopathy. The patient had aortic root dilatation in the absence of overt conotruncal abnormalities or hypertension. Aortic valve was tricuspid. Proximal ascending aorta was normal size but the sinus of valsalva was markedly dilated at 50mm. Other features present in this case included schizophrenia, moderate intellectual disability and facial abnormalities: prominent supra-orbital ridges, abnormal external ears and a bulbous nose. An aortopathy disorders gene panel detected no pathogenic mutations. Array Comparative Genomic Hybridisation (CGH) analysis identified a deletion of chromosome 22 with breakpoints within q11.2 of 2.61 megabase pairs in size which included the TBX1 gene. This was consistent with a diagnosis of 22q11.2DS. The diagnosis of 22q11.2DS is important as there are multisystemic features requiring lifelong monitoring. Although generally de novo deletions, this is an autosomal dominant disorder inferring genetic risk. This adult case of 22q11.2DS with aortic root dilatation raises some important questions: is an echocardiogram at diagnosis alone sufficient in the management of 22q11.2DS? Should we include 22q11.2 / TBX1 gene in aortopathy disorders gene panels?

26. Identifying Long QT syndrome patients in primary care: A population- based case control study

WRH Evans*, RK Akyea, N Qureshi, J Kai, SF Weng

LQTS is an inherited cardiac arrhythmic condition that predisposes patients to syncope and sudden cardiac death. Identification to enable treatment can substantially reduce this risk.

Aim: To identify clinical features which precede diagnosis of Long QT syndrome (LQTS) in primary care and use these to develop a predictive model.

Method: We identified a cohort of 1495 patients with a diagnosis of LQTS from a database of primary care electronic records (CPRD). Each case was matched to 5 controls, accounting for covariates by propensity matching, and clinical features were identified that occurred prior to diagnosis. Multivariable logistic modelling was performed to develop a predictive tool.

Results: A range of clinical features occurring with greater frequency in LQTS patients were identified including: Palpitations (2.22 (1.80,2.74)); epilepsy (1.70 (1.12, 2.56)); irritable bowel syndrome (1.78 (1.41, 2.26)); hypertension (1.64 (1.42,1.91) (OR (95% CI)). A total of 17 clinical features were incorporated into the predictive model with an area under the ROC curve of 0.740.

This is the first study to assess how patients with LQTS present to primary care, with a range of both expected and unexpected clinical features found. This study demonstrates the potential of primary care records to identify patients with an increased likelihood of having a rare disease.

Key words: Genetics, primary care, inherited cardiology, LQTS

PRISM group, Division of Primary care, University of Nottingham.
William.Evans1@nottingham.ac.uk, 07850732023

27. A case of possible germline mosaicism in hypertrophic cardiomyopathy

Bueser, T.[1,3], Walton, A.[4], Nuthoo, S.[1], Carr-White, G.[1] and Robert, L.[2]

Name of presenter: Teofila (Tootie) Bueser

Name of all Departments/Institutions:

[1]Cardiology Department, Guy's & St Thomas' NHS Foundation Trust
[2]South East Thames Regional Genetics Centre, Guy's & St Thomas' NHS Foundation Trust
[3]Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, King's College London
[4]Cardiology Department, King's College Hospital NHS Foundation Trust

Contact details: tootie.bueser@nhs.net , 07738705554

For poster presentation

Hypertrophic cardiomyopathy (HCM) is a genetically and phenotypically heterogenous disease mainly caused by pathogenic variants in sarcomeric protein genes. The mode of inheritance is predominantly autosomal dominant with rare de novo mutations [1]. The first description of germline mosaicism in HCM was described in siblings with a severe phenotype who were carriers for a pathogenic variant in the MYH7 gene (Arg453Cys) [2].

We describe a family where two members carry a pathogenic variant in the TNNT2 gene (c.566C>T) whose parents are non-carriers and phenotypically negative. Paternity has been confirmed and the hypothesis is that this is a case of germline mosaicism. Two other siblings are non-carriers and phenotypically negative for HCM. The proband presented in his late teens with exertional chest pains and significant pre-syncope whilst walking. On echocardiogram, he had a maximal wall thickness of 30 mm and had a flattened blood pressure response to exercise. An internal cardioverter defibrillator for primary prevention was implanted. His sister, also a carrier, remains asymptomatic with no overt signs of HCM.

Whilst tests to confirm germline mosaicism are yet to be completed, this case highlights that genetic counselling should include explanation of possible results and variable penetrance. This may help inform the discussion around systematic genetic screening of siblings of a sporadic proband, even if standard methods fail to clearly detect the mutation in the parents[3].

References:

1.Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C and Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European heart journal*. 2014;35:2733-2779.
2.Forissier JF, Richard P, Briault S, Ledeuil C, Dubourg O, Charbonnier B, Carrier L, Moraine C, Bonne G, Komajda M, Schwartz K and Hainque B. First description of germline mosaicism in familial hypertrophic cardiomyopathy. *J Med Genet*. 2000;37:132-4.
3.Roux-Buisson N, Egéa G, Denjoy I, Guicheney P and Lunardi J. Germline and somatic mosaicism for a mutation of the ryanodine receptor type 2 gene: implication for genetic counselling and patient caring. *EP Europace*. 2010;13:130-132.

28. Dilated cardiomyopathy: Genomic and diagnostic approach.

L. Piherova 1 (lenka.piherova@lf1.cuni.cz, +420224967052); H. Hartmannová 1; K. Hodanova 1; P. Melenovska 1; D. Musalková 1; V. Stranecky 1; M. Kubanek 2; A. Krebsova 2; S. Kmoch 1

Affiliations:

1) Research Unit for Rare diseases, First Faculty of Medicine, Charles University, Prague 2, Czech Republic; 2) Institute for Clinical and Experimental Medicine (IKEM), Department of Cardiology, Prague, Czech Republic

Key words: Dilated cardiomyopathy, Exome sequencing, CNV

Abstract:

Cardiomyopathy is a disease of the heart muscle associated with a disorder of its function. This is a heterogeneous group of diseases with various clinical signs that can ultimately lead to heart failure. Subset of cardiomyopathies are genetically conditioned.

The use of the whole exome sequencing is currently one of the most effective tools for elucidating the genotype of individual patients.

We have successfully used this method for studying of genetic architecture of dilated cardiomyopathy cohort of the 460 patients. Most frequently affected genes were TTN (18%), FLNC (4%), MYBPC3 (4%), MYH7 (4%), DSP (4%), RBM20 (3%). We have also found CNV variants (around 2% in our cohort) in DMD, LAMP2, FLNC, LMNA and MYH7 genes, which were predicted to cause major structural and functional abnormalities of the affected genes.

Successful molecular biology diagnostic and helps to identify the risk of occurrence of the disease in the family and to ensure prenatal diagnosis. In selected cases, the phenotype can also be studied on cell models, which contributes to the understanding of the molecular mechanism of the disease and allows a more accurate interpretation of border clinical or laboratory findings.

29. Variant re-interpretation in next-generation sequencing data increases diagnostic yield in Dutch cardiomyopathy patients

Yvonne J. Vos[1], Mohamed Z. Alimohamed, Lennart F. Johansson, Helga Westers, Richard J. Sinke, Rolf H. Sijmons, Birgit Sikkema-Raddatz, Jan D.H. Jongbloed, Paul A. van der Zwaag

University of Groningen, University Medical Center Groningen, Department of Genetics, Groningen, the Netherlands

Background

Next-generation sequencing (NGS) is used for clinical evaluation of patients with cardiomyopathies, because it allows for simultaneous screening of multiple genes. Diagnostic yield, pathogenic and likely pathogenic variants correlated to the patients phenotype, differ due to differences in populations studied and variant interpretation.

Objectives

(1) o determine the yield of our targeted NGS gene panel used in routine clinical diagnostics in a Dutch cohort of cardiomyopathy patients. (2) To examine the effect of pathogenicity reassessment for variants of unknown significance based on published statistical thresholds. **Methods**

Patients (N=2002) referred for genetic analyses underwent DNA testing of 55-61 genes associated with cardiomyopathies. Variants (single nucleotide and copy number variants) were classified using routine diagnostic criteria. Variants of unknown significance in specific genes, intolerant to variation and having high probability to be disease causing, were identified and reclassified.

‘The Global Familial Heart Challenge’

Professor Dhavendra Kumar, The Genomic Medicine Foundation (UK);

The William Harvey Research Institute, Queen Mary University of London, UK

Familial and inherited cardiovascular diseases are diverse and affect all irrespective of the geographic and ethnic origin. It is a global phenomenon and requires a world wide high level strategic health approach. The whole group of conditions poses a major global health challenge. The proposed Global Familial Heart Challenge (GFHC) is a new international initiative for raising awareness, empowering clinicians, health care providers and public for developing regional and country specific health networks for information, data resource and targeted specialist health service provision for multi-disciplinary care for patients and families affected with familial and inherited heart disease.

Aim

To set up and develop the coordinated global network to deal with medical and health challenges of the familial / inherited heart disease.

Objectives and Principles

The Global Familial Heart Challenge (GFHC) is a network of a number of clinical establishments, genetic/genomic laboratories, research centers and patient/ family support groups committed to caring and supporting patients and families affected with a familial/ inherited heart disease organized on the following core principles:

- Each individual center, partner or professional contributes on voluntary basis
- No direct access to any patient clinical or research data or information
- Any information or data shared by the source organization is secured
- Functions through the consortium of several clinicians, health professionals, laboratory scientists, researchers and patient/ family support workers- each group contributing on a participative and consultative basis
- The consortium is arranged on Regional and Country node basis to ensure that national regulatory and legal requirements are adhered to as well as all relevant social, cultural and religious norms are taken into account
- Administered by the appointed executive team selected from the consortium membership

For information and membership of GFHC-

Contact Prof. Dhavendra Kumar, CEO & Medical Director,
The Genomic Medicine Foundation (UK) www.genomicmedicine.org

[illegible]

[illegible]

[illegible]

1. [illegible]
2. [illegible]
3. [illegible]
4. [illegible]

[illegible]

Background: T-peak-to-end (Tpe) interval on the electrocardiogram (ECG) is a measure of myocardial repolarization and prolongation is associated with increased ventricular arrhythmic risk. However, our understanding of the electrophysiological mechanisms underlying this marker remains limited. Our main objective was to investigate the genetic basis and biology underlying the Tpe interval.

Methods: ECG recordings from 71,338 volunteers in the UK Biobank study were analyzed. Resting Tpe was measured as the time interval between the T-wave peak and the T-wave end at rest. A genome-wide association study (GWAS) was performed and genetic risk scores (GRSs) were tested for association with ventricular arrhythmic events in 342,819 unrelated individuals in the UK Biobank study.

Results: We identified twenty-eight loci for resting Tpe, eight of which are not associated with other ECG traits. Bioinformatics analyses indicated that ventricular repolarization and cardiac conduction/contraction were key modulators of the Tpe interval. Genetic risk analysis showed that individuals in the top 5% of the GRS have a ~32% higher risk of ventricular arrhythmias or cardiac arrest compared to the remaining individuals (P = 2.2 x 10^{-3}).

Conclusion: Our findings unveil specific modulating genes involved in ventricular arrhythmogenesis and strengthen the relevance of the Tpe interval for risk prediction.

Keywords: Tpe interval, ventricular arrhythmic risk, genetic risk score, genetic analysis, electrocardiogram, general population

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

"The 7th International Cardiovascular Genetics & Genomics Conference"

'Clinical Cardiology in the Genome Era'

4-5 December 2019, York, England, UK

Approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 12 category 1 (external) CPD credits

Conference Evaluation (Confidential)

Name…..…… /Hospital or Institution……

Affiliation: Cardiologist/Clinical Geneticist/Cardiac Nurse/Genetic Counsellor/Laboratory Scientist/Research Fellow/ Academic/ Public Health/ Other (please specify)

Telephone/ Email (optional)……

Session	Title/Speaker	Satisfactory	Good	Excellent	Any other Comments
1	Phenotype-genotype ontology of inherited cardiovascular conditions: Congenital Heart Disease				
	Ontology of Myocardium phenotypes				
	Primary lymphatic anomalies- an update				
	Role of Myocardin in smooth and cardiac muscle development				
Plenary 1	'Genomics led personalised prescribing in cardiovascular				

	medicine'				
2	**Sarcomere- novel genes and related molecules**				
	MYH7 variant in Egyptian HCM patients				
	Titin and related genes/molecules				
	Dystrophin & related molecules				
3	**Brugada syndrome- Mendelian, Oligogenic or Multigenic?**				
	Genomic complexity of atrial fibrillation				
	Whole genome and transcriptome sequencing of post-mortem cardiac tissues from sudden cardiac death victims				
	The Egyptian Collaborative Cardiac Genomics (ECCO-GEN): Defining a Healthy Volunteer Cohort				
Plenary 2	**The Sir William Harvey Oration 'Life long pursuit of Inherited Cardiovascular Conditions'**				
4	**The Miles Frost Hypertrophic Cardiomyopathy Prevention- a model for Preventive (Community/Public Health) Cardiology**				
	Outcomes of the next generation genome diagnosis for inherited cardiac conditions				
	Hypertrophic Cardiomyopathy & Pregnancy Outcomes in North India				
	Multi-Disciplinary team for delivering the NHS cardiovascular genomic medicine service				
5	**Polygenic score and complex cardiac conditions**				
	Stroke genetics & genomics in clinical arena				
	Systemic Hypertension- outcomes of genomic studies				
	Genomic insights in aortic &				

	arterial diseases				
Plenary 3	**'The Genomic Revolution in Pediatric Clinical Cardiology'**				
6	**Validating electronic health records (EHR) cardiovascular phenotypes by the UK Phenomics platform**				
	Pertinent Issues in cardiovascular diagnostic genomic testing				
	Challenge of variant classification in cardiovascular medicine: The example of hypertrophic cardiomyopathy				
	Development of the Indian Inherited Cardiovascular Conditions Database				
7	**Novel therapeutic advances in arrhythmogenic cardiomyopathy**				
	Stem cell and related therapeutic advances in hypertrophic cardiomyopathy				
8	**Heart failure, severe arrhythmia and sudden cardiac death in Marfan syndrome and related heritable thoracic aortic diseases**				
	Atypical *COL3A1* variants (glutamic acid to lysine) cause vascular Ehlers-Danlos Syndrome with a consistent phenotype of tissue fragility and skin hyperextensibility				
	Genome sequencing for inherited cardiac conditions: analysis of 201 cardiovascular patients recruited through the 100,000 Genomes project by the West of England and South West NHS Genomic Medicine Centres.				
	Major Genetic Contributors to Non-syndromic Tetralogy of Fallot				
	Identifying Long QT syndrome patients in primary care: A population- based case control study				
	Biallelic *PPP1R13L*-associated				

	paediatric dilated cardiomyopathy: expanding the phenotypic spectrum				
Plenary 4	**'Dilated Cardiomyopathies- new paradigms for cardiovascular genomic medicine'**				

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

VII INTERNATIONAL CARDIOVASCULAR GENOMIC MEDICINE CONFERENCE

"CLINICAL CARDIOLOGY IN THE GENOME ERA"

4-5 DECEMBER 2019, YORK, ENGLAND, UK

Approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 12 category 1 (external) CPD credits

CERTIFICATE OF ATTENDANCE

This is to confirm that Prof/ Dr. / Mr/ Ms

_____

Participated in this conference as Organizer/ Faculty/ Speaker/ Presenter/ Delegate

Professor Dhavendra Kumar
Chair- Organizing & Scientific Committees, VII ICVGM- 2019

The Global Familial Heart Challenge

Professor Dhvendra Kumar
William Harvey Research Institute
Queen Mary University of London, UK
St. Barts Hospital, London, UK
The Genomic Medicine Foundation (UK)

Kumard1@cf.ac.uk; d.kumar@qmul.ac.uk ; genomicmedicine@yahoo.co.uk

The Global Familial Heart Challenge

"The Global Familial Heart Challenge (GFHC) is a new international initiative to raise awareness, empower and educate medical and healthcare providers on specialist health service provision on Familial & Inherited cardiovascular conditions"

Familial/Inherited Heart Diseases

- Familial / Inherited cardiovascular diseases are global
- Affect *all* irrespective of geographic and ethnic origin
- Global phenomenon- requires a world wide high level strategic health approach
- Familial/ Inherited heart diseases- a major global challenge including high 'sudden death' risk
- Approximately 1 in 3 patients seeking primary and specialist healthcare could have one or more of these conditions
- Huge burden on healthcare provision with diverse socio-economic implications

AIM

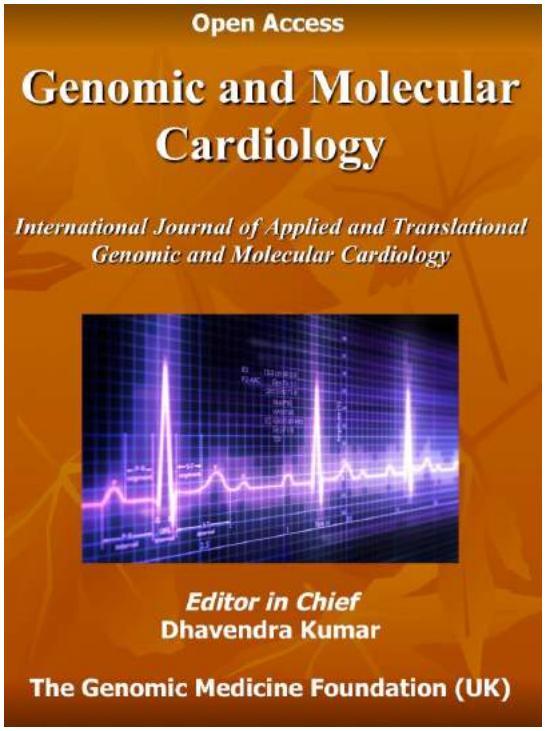
"To set up and develop the coordinated global network to deal with medical, health and socio-economic challenges of familial and inherited heart diseases"

Objectives

1. Establish a consortium of cardiologists, healthcare professionals, laboratory scientists and patient & family support groups engaged with inherited familial heart diseases
2. Identify and agree to the key healthcare challenges of the family and inherited heart disease- clinical diagnosis, laboratory genetic genomic diagnosis, multidisciplinary care and healthcare advice, prevention and support
3. Organize the Global Familial Heart Challenge (GFHC) consortium on a world-wide basis using the Regional and Country mode format.
4. Contribute and coordinate development of databases for clinical and research purposes with specific focus on phenotype annotation and validation of gene specific or genome wide variants
5. Set up and provide on-line access to a 'consumers'- professionals, partners, patients and public seeking validated and validated information on common and rare familial/ inherited heart diseases

GFHC Four Focus Groups- the 4 C's

1. **C**ore infrastructure
2. **C**are- multi-disciplinary team
3. **Counseling**- multi-levels & dynamic
4. **C**ommunity- aware & prevent



'GENOMIC AND MOLECULAR CARDIOLOGY'

Open Access International Journal of Applied and Translational Genomic and Molecular perspectives of Cardiovascular Medicine and Surgery

Editor in Chief:

Professor Dhavendra Kumar

MD DSc FRCP FRCPCH FACMG

Consultant in Clinical Genetics/ Cardiovascular Genetics, Institute of Medical Genetics, *University Hospital of Wales, Cardiff, UK*

Manuscripts of original research papers, meta-analysis, review articles, commentaries and opinions and conference reports are invited for publication in ***Genomic and Molecular Cardiology (GMC).*** All manuscripts should be submitted online as an email attachment to JournalGMC@genomicmedine.org. Submitted manuscripts are independently peer-reviewed and all accepted manuscripts are published online subject to copyright agreement and open access publication charge.

The journal (GMC) focuses on delineation of the clinical phenotypes, new genes and variants, genotype-phenotype correlations, basic and clinically applied molecular genetics, next generation sequencing and new pharmaceutical and interventional therapeutic advances. The original cardiovascular research will highlight the ***OMICS*** (proteomics, transcriptomics, metabolomics, functional genomics and others) as well as clinical trials in the burgeoning field of cardiovascular pharmacogenomics. The journal also features current and comprehensive reviews in the areas of recent advances in cardiovascular development, Mendelian cardiovascular conditions, complex cardiovascular genomics, new diagnostic and therapeutic progress, and controversies in cardiovascular genetics & genomics. The journal also publishes pertinent clinical case reports, clinical audit outcomes, book reviews, and letters to the editor.

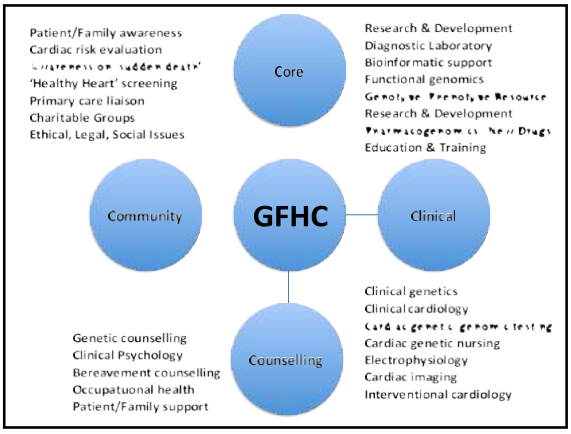
The journal is open-access as per terms and conditions available from the publishers the Genomic Medicine Foundation (UK) Ltd, a *not-for-profit* company registered in England and Wales (Registered Number 8749919). For all enquiries and information please visit www.genomicmedicine.org or JournalGMC@genomicmedicine.org.

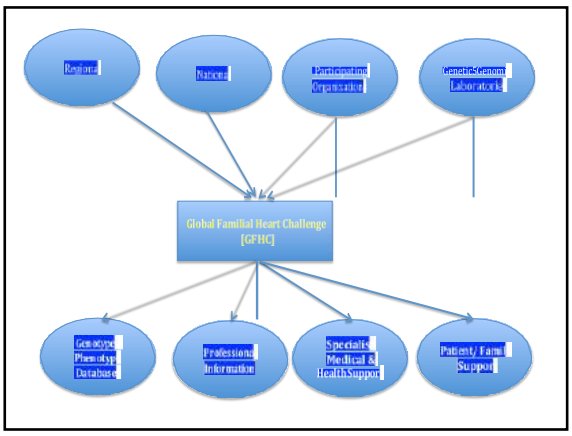
Submission of manuscripts:

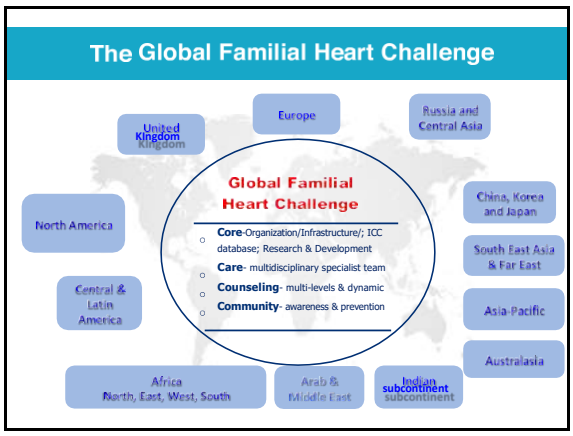
Manuscripts of original research papers, review articles, commentaries and opinions and conference reports are invited for publication in **Genomic and Molecular Cardiology**. All manuscripts should be submitted online as an email attachment to *JournalGMC@genomicmedicine.org*. All manuscripts should follow the usual format and include: the title, authors, institute affiliations, name/address of the corresponding author, selection of search engine key words (not more than 10), name/ address of relevant ethical approval authority, declaration on conflict of interest, statement on commercial/ financial benefits and copyright authorization for any illustrations, tables or part of the text included in the manuscript. References should be cited in the text with author and year; use suffix et al for more than 2 authors in the reference cited. All references should be listed in alphabetical order. All manuscripts are independently peer-reviewed and final decision is made by the editor in chief reflecting views of the lead-editor (usually a member of the editorial board or a guest editor) and external reviewers. All accepted manuscripts are published online subject to copyright agreement with the publisher and payment of open access publication charge, advised with the copyright instructions. The publication charge may be waived on the recommendation of the editor in chief. The open access tariff is available on request, however the specific amount will be advised on acceptance of the manuscript. All open access paid published material will become globally accessible. However, an individual reader, organization or Institution may access any article on payment of a fee.

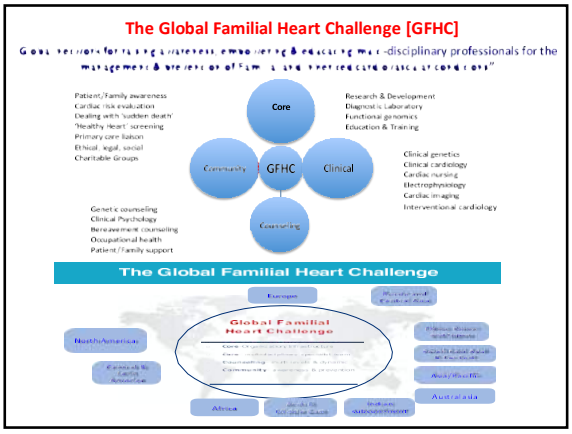
Corporate information:

'Genomic and Molecular Cardiology' is published by The Genomic Medicine Foundation (UK) Ltd, a not- for-profit company registered in England and Wales (*Registered Number 8749919*). The publisher holds all legal rights and acquires all financial or any other benefits of any published material in the journal. For all enquiries and information please visit *www.genomicmedicine.org* or contact direct the Editor in Chief (*JournalGMC@genomicmedicine.org*)









GFHC Partners & Collaborators

- The Genomic Medicine Foundation (UK)
- International Scientific Advisory Committee of the Human Variome Project (HVP)
- Genomic Alliance for Global Health (GA4GH)
- European ICC Consortium
- ClinVar/ ClinGen- **NIH/Harvard**

Summary

- Familial and Inherited cardiovascular diseases pose a significant global health challenge
- Joint concerted efforts are needed for raising awareness, early diagnosis, detection of high risk individuals, family/community level screening and prevention of major complications including 'sudden death'
- 'Global Familial Heart Challenge' is a global initiative

WITH THANK TO OUR SPONSORS

This meeting has been supported through industry sponsorship, however, they have had no involvement in setting the agenda, topics or selection of the speakers

GOLD SPONSOR

British Heart Foundation

SILVER SPONSOR

Amicus Therapeutics®

Alnylam® PHARMACEUTICALS

BRONZE SPONSOR

AKCEA™ THERAPEUTICS
A subsidiary of Isis Pharmaceuticals, Inc.

Takeda