in this study, we conclude that PFO device closure should be offered cautiously and only after careful multi-disciplinary assessment.

Conflict of Interest None to declare

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UPDATE ON FAMILIAL THORACIC AORTIC ANEURYSM DISEASE IN THE 100,000 GENOMES PROJECT: SPACE FOR DISCOVERY

¹Catherine Francis*, ²Yalda Jamshidi, ³George Gkoutos, ⁴Bernard Keavney, ⁵Paul Clift, ⁶Tom Fowler. ¹National Heart & Lung Institute, Imperial College London; ²Genetics Research Centre, Molecular & Clinical Sciences Institute, St George's University of London; ³Institute of Cancer and Genomic Sciences, University of Birmingham; ⁴Faculty of Biology, Medicine and Health, University of Manchester; ⁵Department of Cardiology, Queen Elizabeth Hospital Birmingham; ⁶Genomics England, London, UK

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Background The 100,000 Genomes Project offers an unprecedented opportunity to leverage whole genome sequencing data to characterise the hereditary basis of Familial Thoracic Aortic Aneurysm Disease (FTAAD). FTAAD is a heterogeneous group of syndromic and isolated aortopathies. The genetic basis of this presentation often remains undiscovered.

Purpose To define the FTAAD cohorts available in the 100,000 Genomes Project and assess the current diagnostic yield and space for future discovery.

Materials and methods As of February 2019, 536 probands with FTAAD and HPO terms for thoracic aortic disease have been recruited to the 100,000 Genomes Project. Inclusion criteria included:

- Thoracic aortopathy <50 years with no additional risk factors or
- Marfan syndrome with no identified FBN1 mutation or
- Loeys-Dietz syndrome or related condition, and
- Negative initial genetic screening to include FBN1, TGFBR1&2, ACTA2 where appropriate.

Whole genome sequencing, quality control and filtering was carried out by Genomics England as previously

Abstract 142 Figure 1 Genetic heterogeneity of FTAAD: Pie chart showing validated aortopathy genes in which rare, protein-altering variants are found

described. Aortopathy genes are defined in PanelApp, an expert-curated gene list with validated associations with FTAAD. Genes curated for only skeletal phenotypes (eg FBN2, FLCN) with no evidence for aortic involvement were excluded. Tier 1 variants are rare and protein-truncating; tier 2 variants are rare and protein-altering. Tiered variants were excluded if Clinvar status was benign, or if they were not fully penetrant.

Results The cohort has a mean age of 44 years (range 0–79). 110 probands were <30 years old at disease onset. 113 probands had a history of aortic dissection. 96 had additional aortic valve abnormalities, with 36 reported as bicuspid. Only 22 were reported to have significant AR or AS. Skeletal abnormalities were prevalent, with 66 having sternal abnormalities.

Only 8 Tier 1 variants in validated aortopathy genes were reported in this cohort. These were in BGN, FBN1, LOX, MYH11, MYLK, TGFB2 and TGFBR1 (see table1). This

Abstract 142 Table 1 Variants in curated aortopathy gene panel identified in FTAAD probands

TIER1 (protein-truncating rare variants)			
Gene	Variant (GRCh38)	Consequence	Pathogenicity (ClinVar or clinical team)
LOX	5:122070160T>TA	Frameshift	Likely Pathogenic
	5:122077495TC>T	Frameshift	Likely Pathogenic
FBN1	15:48645574C>T	Splice donor (LoF)	Not reported
BGN	X:153508247G>A	Splice acceptor (LoF)	Likely pathogenic
TGFBR1	9:99146492GC>G	Frameshift	Not reported
TGFB2	1:218441264C>T	Stop gained	Likely pathogenic (similar variants same codon)
MYH11	16:15721419T>TA	Frameshift	Likely pathogenic; de novo
MYLK	3:12368222ACT>A	Frameshift	Likely pathogenic

defines a diagnostic yield of just 8/536 (6%) in this patient group, using known aortopathy gene panels. Surprisingly, none of these variants were found in probands under 30 at disease onset.

There were 68 classic trios in this cohort (proband + mother and father). However, just one of these has a clearly pathogenic de novo variant identified (in MYH11). There were just 2 Tier 2 variants of uncertain significance (VUS) in aortopathy genes in other trios. 10 larger family structures have yielded no clear pathogenic candidates to date. The majority of the cohort are recruited as singletons.

75 Tier 2 variants have been identified to date in 19 aortopathy genes (see figure 1). Just 1 of these (in LOX) can be classified as likely pathogenic. The remainder are VUSs.

Conclusion In this genetically pre-screened cohort with FTAAD, genetic diagnosis remains elusive. The variety of genes in which protein-altering variants are found highlights the genetic heterogeneity of this condition. We plan further systematic studies of the family structures available in the 100,000 Genomes Project and case:control studies to further elucidate the genetic architecture of FTAAD. The negative findings to date, particularly in probands with young-onset aortopathy, make it likely that responsible genes are yet to be discovered in many cases.

This research was made possible through access to the data and findings generated by the 100,000 Genomes Project.

Conflict of Interest None

Acute Coronary Syndromes

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A PIVOTAL ROLE FOR NRF2 IN ENDOTHELIAL DETACHMENT— IMPLICATIONS FOR ENDOTHELIAL EROSION OF STENOTIC PLAQUES

¹Sandro Satta*, ²Michael McElroy, ¹Alex Langford-Smith, ¹glenn Ferris, ³Jack Teasdale, ⁴Yongcheol Kim, ⁵Giampaolo Niccoli, ⁶Ajime Tanjeko, ⁷Jef Serré, ³Georgina Hazell, ³Graciela Sala-Newby, ¹Ping Wang, ³Jason Johnson, ¹Martin Humphries, ⁷Ghislaine Gayan-Ramirez, ⁸Peter Libby, ⁵Filippo Crea, ¹Hans Degens, ⁹Frank Gijzen, ¹⁰Tom Johnson, ¹Amir Keshmiri, ¹Yvonne Alexander, ³Andrew Newby, ¹Stephen White. ¹Manchester Metropolitan University; ²University of Manchester; ³University of Bristol; ⁴Chonnam National University Hospital; ⁵Catholic University of the Sacred Heart - Rome; ⁶KULeuven; ⁷KULeuven; ⁸Harvard Medical School; ⁹Erasmus MC; ¹⁰Bristol Heart Institute, Bristol Royal Infirmary

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Introduction Endothelial erosion of atherosclerotic plaques and resulting thrombosis causes approximately 30% of acute coronary syndromes (ACS). Plaque erosion is most frequently observed in smokers, which induces endothelial dysfunction, partially through elevated circulating mediators of inflammation, such as tumour necrosis factor- α (TNF α), as well as free radical, oxidative and chemically induced damage. We have previously demonstrated that fresh aqueous cigarette smoke extract (CSE) increases the expression of Nrf2-target genes in human coronary artery endothelial cells, which was further increased by TNF α in a shear stress-dependent manner.

Methods The haemodynamic environment significantly regulates both plaque development and endothelial function, therefore we determined the haemodynamic environment permissive for plaque erosion. We reconstructed the coronary artery geometries from 17 heart attack patients with thrombi overlying intact fibrous caps (OCT-defined erosion) and performed computational fluid dynamic analysis. We created an in vitro model of erosion by culturing human coronary artery endothelial cells under elevated flow and exposing them to CSE and TNF α .

Results We identified that in 14 cases of OCT-defined erosion occurred in areas of stenosis, with the preeminent flow feature being elevated flow. Exposing human coronary artery endothelial cells to elevated flow, CSE and TNF α induced significant endothelial detachment, which was enhanced by pharmacological activation of the antioxidant system controlled by transcription factor Nrf2. The Oxidative Stress Growth INhibitor genes OSGIN1 and OSGIN2 were both maximally upregulated under these conditions and also in the aortas of mice exposed to cigarette smoke. Adenoviral overexpression of OSGIN1+2 in static culture resulted in cell cycle arrest in S-phase (5.5-fold increase, $p = 0.003$), with a significant increase in the number of multinucleated cells (4.5-fold, $p = <0.001$). Immunocytochemical analysis indicated loss of focal adhesions and stress fibres, dysregulation of autophagy and induction of senescence in HCAEC, with a significant increase in senescence-associated β -galactosidase staining (6.7-fold, $p = <0.001$) and P16 expression (3.2-fold, $p = 0.035$). Importantly, overexpression of either Nrf2, or OSGIN1+2 induced cell detachment, which was independent of apoptosis, and could be rescued by inhibition of HSP70 nucleotide binding site using VER-155008, or AMPK activation using Metformin.

Conclusions In summary, we have defined the haemodynamic environment in which endothelial erosion occurs and identified that smoking-induced hyperactivation of Nrf2 may promote endothelial cell detachment, contributing to plaque erosion overlying stenotic plaques, through the combined upregulation of OSGIN1 and OSGIN2. This highlights a completely novel mechanism potentially contributing to 30% of ACS and suggests possible therapeutic avenues for further investigation.

Conflict of Interest none

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HIGH-SENSITIVITY CARDIAC TROPONIN AND THE FOURTH UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

¹Andrew Chapman*, ²Philip Adamson, ¹Anoop Shah, ¹Atul Anand, ¹Fiona Strachan, ¹Kuan Ken Lee, ¹Amy Ferry, ³Dennis Sandeman, ¹Catherine Stables, ⁴David Newby, ¹Nicholas Mills. ¹University of Edinburgh; ²University of Otago, Christchurch; ³NHS Fife; ⁴British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh

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Background The Universal Definition of Myocardial Infarction recommends the 99th centile diagnostic threshold using a high-sensitivity cardiac troponin (hs-cTn) assay and