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

Abstract 142

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

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 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, TGFBR2 and TGFB1 (see table1). This

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant (GRCh38)</th>
<th>Consequence</th>
<th>Pathogenicity (ClinVar or clinical team)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOX</td>
<td>5:122070160T&gt;TA 5:122077495TC&gt;T</td>
<td>Frameshift Frameshift</td>
<td>Likely Pathogenic Likely Pathogenic</td>
</tr>
<tr>
<td>FBN1</td>
<td>15:48645574C&gt;T</td>
<td>Splice donor (LoF)</td>
<td>Not reported</td>
</tr>
<tr>
<td>BGN</td>
<td>X:153508247G&gt;A</td>
<td>Splice acceptor (LoF)</td>
<td>Likely pathogenic</td>
</tr>
<tr>
<td>TGFBR1</td>
<td>9:99146492GC&gt;G</td>
<td>Frameshift</td>
<td>Not reported</td>
</tr>
<tr>
<td>TGFB2</td>
<td>1:218441264C&gt;T</td>
<td>Stop gained</td>
<td>Likely pathogenic (similar variants same codon)</td>
</tr>
<tr>
<td>MYH11</td>
<td>16:15721419T&gt;TA</td>
<td>Frameshift</td>
<td>Likely pathogenic; de novo</td>
</tr>
<tr>
<td>MYLK</td>
<td>3:12368222ACT&gt;A</td>
<td>Frameshift</td>
<td>Likely pathogenic</td>
</tr>
</tbody>
</table>
A PIVOTAL ROLE FOR NRF2 IN ENDOTHELIAL HIGH-SENSITIVITY CARDIAC TROPONIN AND THE GENETIC HETEROGENEITY OF AORTOPATHY GENES

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-alpha (TNFα), 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 TNFα 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 TNFα.

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 and exposing them to CSE and TNFα 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

Acute Coronary Syndromes

A PIVOTAL ROLE FOR NRF2 IN ENDOTHELIAL EROSION OF STENOTIC PLAQUES

1Sandro Satta*, 2Michael McClory, 3Alex Langford-Smith, 4glenn Ferris, 3Jack Teasdale, 4Yongchun Lu, 5Ming Xiao, 6Pamela Taylor, 7Jeff Serres, 2Giorgina Hazel, 8Giacomo Sala-Newby, 9Ping Wang, 3Jason Johnson, 10Martin Humphries, 75Tier 2 variants have been identified to date in 19 aortopathy genes (see figure 1). Just 1 of these (in LOX) aortopathy genes (see figure 1). Just 1 of these (in LOX).

Methods

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

Background

The Universal Definition of Myocardial Infarction

1Andrew Chapman*, 2Philip Adamson, 3Anoop Shah, 4Atul Anand, 5Fiona Strachan, 6Kuan Ken Lee, 7Amy Feny, 8Dennis Sandeman, 9Catherine Stables, 10David Newby, 11Nicholas Mills. 
University of Edinburgh; 2University of Otago, Christchurch; 3NHS Fife; 4British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh

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 TNFα.

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 and exposing them to CSE and TNFα 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

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

1Andrew Chapman*, 2Philip Adamson, 3Anoop Shah, 4Atul Anand, 5Fiona Strachan, 6Kuan Ken Lee, 7Amy Feny, 8Dennis Sandeman, 9Catherine Stables, 10David Newby, 11Nicholas Mills. 
University of Edinburgh; 2University of Otago, Christchurch; 3NHS Fife; 4British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh

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 TNFα.

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 and exposing them to CSE and TNFα 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