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

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

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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-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, 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

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

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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