Background Sarcoidosis is a chronic systemic disease associated with cardiovascular manifestations. Although various inflammatory conditions have become recognized as non-traditional risk factors for cardiovascular disease (CVD), the risk profiles in sarcoidosis remain uncharacterised due to its rarity. Using a big data approach we evaluated the burden of CVD on patients with sarcoidosis.

Methods The Algorithm for Comorbidities, Associations, Length of Stay and Mortality (ACALM) study consists of 1816230 patients admitted hospitals in England between 2000–2014. All patients admitted with sarcoidosis were compared to age and gender matched control groups and multivariate logistic regression analyses were used to evaluate the risk of CVD.

Results 902 sarcoid patients were compared to an age and gender matched control group of 9020 patients (mean age 50±15, 50.4% male). Both groups were predominantly Caucasian (sarcoid 50.3% vs. control 78%) but as expected, higher proportions of sarcoid patients were Afro-Caribbean (18.2% vs. 3.0%) and South Asian (20.2% vs 7.3%). Sarcoid patients were significantly more likely to have heart failure (Odds ratio, OR 2.2), chronic kidney disease (OR 2.9), hypertension (OR 1.7), hyperlipidaemia (OR 1.3), and type 2 diabetes (OR 2.0). They were less likely to have acute coronary syndrome (OR 0.4).

Conclusion Sarcoidosis is associated with a marked increase in heart failure and kidney disease, as well as a range of traditional CVD risk factors which need to be managed. These results are illustrated in Table 1.

Conflict of Interest None

Valve Disease/Pericardial Disease/Cardiomyopathy

121 RE-EVALUATING THE GENETIC CONTRIBUTION OF MONOGENIC DILATED CARDIOMYOPATHY

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Introduction Dilated cardiomyopathy (DCM) is genetically heterogeneous, with >100 purported disease genes tested in clinical laboratories. However, many genes were originally identified based on candidate-gene studies that did not adequately account for background population variation. Here we define the frequency of rare variation in 2538 DCM patients across protein-coding regions of 56 commonly tested genes and compare this to both 912 confirmed healthy controls and a reference population of 60,706 individuals in order to identify clinically interpretable genes robustly associated with dominant monogenic DCM.

Methods We used the TruSight Cardio sequencing panel to evaluate the burden of rare variants in 56 putative DCM genes in 1040 DCM patients and 912 healthy volunteers processed with identical sequencing and bioinformatics pipelines. We further aggregated data from 1498 DCM patients sequenced in diagnostic laboratories and the ExAC database for replication and meta-analysis.

Results Specific variant classes in TTN, DSP, MYH7 and LMNA were associated with DCM in all comparisons. Variants in BAG3, TTN2, TPM1, NEXN and VCL were significantly enriched specific patient subsets, with the last 3 genes likely contributing primarily to early-onset forms of DCM. Overall, rare variants in these 9 genes potentially explained 19–26% of cases. Whilst the absence of a significant excess in other genes cannot preclude a role in disease, such genes have limited diagnostic value since novel variants will be uninterpretable and therefore non-actionable, and their diagnostic yield is minimal.

Conclusion In the largest sequenced DCM cohort yet described, we observe robust disease association with 9 genes, highlighting their importance in DCM and translating into high interpretability in diagnostic testing. The other genes evaluated have limited value in diagnostic testing in DCM. This data will contribute to community gene curation efforts, and will reduce erroneous and inconclusive findings in diagnostic testing.

Conflict of Interest None

122 ENDOTHELIAL LOSS AS A CAUSE OF IMPAIRED MYOCARDIAL PERFUSION RESERVE IN SEVERE AORTIC STENOSIS

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Introduction Impaired myocardial perfusion reserve occurs in pressure overload hypertrophy such as in severe aortic stenosis (AS) despite unobstructed epicardial coronaries. However the pathological mechanisms underlying this are poorly understood. We sought to assess myocardial perfusion reserve in severe AS by stress perfusion cardiovascular magnetic resonance (CMR), and examine the findings in relation to the histological evidence of vascular changes in the myocardium.

Methods Fourteen patients with severe AS and unobstructed epicardial coronaries underwent adenosine stress perfusion CMR before and 6 months after surgical aortic valve replacement (AVR). Myocardial biopsies were obtained during AVR and stained using CD31+ for endothelium, smooth muscle actin (SMA) for smooth muscle, and picrosirius red for fibrosis. Nine age- and sex-matched post-mortem myocardial samples served as histological controls.

Results When compared to controls, the myocardium of patients with severe AS had reduced vessel density, total quantity of SMA+ve and CD31+ve, in addition to the expected increase in fibrosis. (Figure 1) There was absence of CD31+ve endothelium in SMA+ve arterioles, indicating endothelial loss. Importantly, patients with an aortic valve area (AVA) ≤0.8cm² had greater endothelial loss compared to those with an AVA >0.8 and ≤1.0cm² (1.34±0.44% vs 2.84±1.03%, p=0.006), and endothelial loss also correlated with myocardial perfusion reserve index (MPRI), r=0.66, p=0.019. MPRI improved significantly post AVR (from 0.95±0.17 to 1.50±0.43, p=0.018).