Sex differences in metabolic and inflammatory profiles in arrhythmogenic cardiomyopathy: insights from myocardial and plasma omics

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Background: Arrhythmogenic cardiomyopathy (ACM) is characterised by fibrofatty myocardial replacement, ventricular arrhythmias and in some cases, heart failure. Experimental data implicate mitochondrial dysfunction as a potential driver of fibrosis. Mitochondrial injury can increase reactive oxygen species, activate DNA damage signalling and trigger innate and adaptive immune responses. Furthermore, mitochondrial biology and immune regulation mechanisms may differ between women and men with ACM.
Purpose: To characterize metabolic, mitochondria and inflammatory pathway alterations in ACM myocardium and to explore sex-specific molecular patterns.
Methods: RNA sequencing was performed in myocardial tissue from 10 definite ACM patients and 10 control patients. Gene set enrichment analysis (GSEA) assessed directional pathway changes in ACM versus controls. In an independent cohort, plasma proteomics in 38 ACM patients and 24 controls quantified 360 proteins using Proximity Extension Assay. Sex-stratified analyses of ACM patients (13 women, 25 men) used standard comparative statistics and gene-set enrichment.
Results: In myocardial samples from ACM patients (80% with desmosomal mutation), we observed broad transcriptional remodelling versus healthy controls, with consistent activation of mitochondrial stress, and DNA-damage pathways together with altered inflammatory signalling (Figure 1). In the cohort of 38 ACM patients (65% with desmosomal mutation) median age was 51 (IQR 43–60) years and ARVC 2010 Task Force score 7 (IQR 6–8); women and men showed no major differences in age, BMI or ventricular function. Proteomic and gene-set analyses nevertheless revealed significant sex-related differences ($p<0.05$): women had higher levels of proteins linked to metabolism, hormone signalling and myocardial stress whereas men showed higher signals of markers related to systemic inflammation, immune activation and extracellular-matrix turnover (Figure 2).
Conclusion: Myocardial transcriptomics in ACM hearts indicate that mitochondrial dysfunction, DNA-damage signalling and inflammation form distinct disease mechanisms. In a larger plasma cohort, sex-stratified proteomics suggest that these processes are engaged differently in women and men, with a more metabolic/mitochondrial stress- oriented profile in women and a more inflammatory/immune-dominant profile in men.

gene set enrichment analysis in ACM

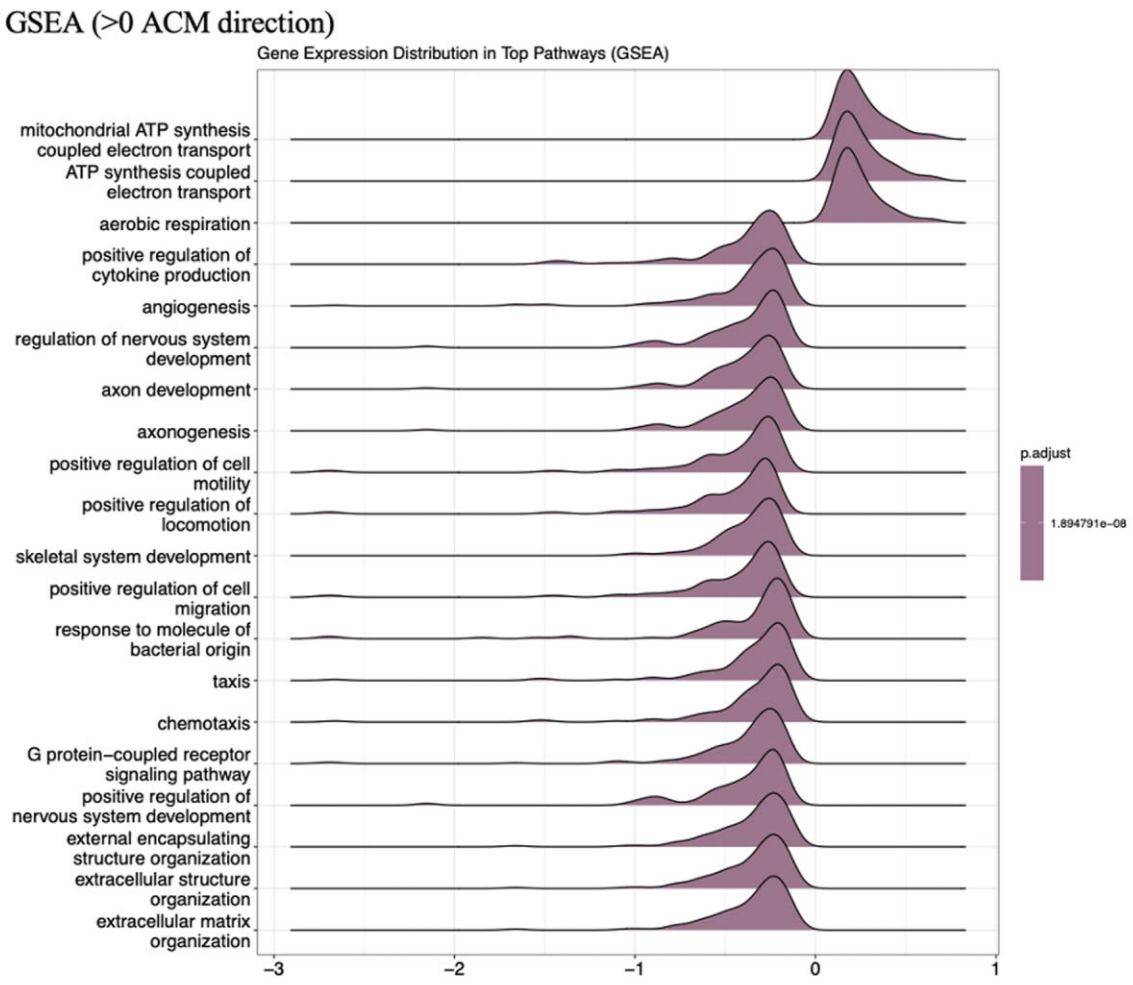

Figure 1. Top pathways enriched in myocardial tissue of ACM vs. controls by gene set enrichment analysis; gene expression distributions with adjusted p-values.

Volcano plot of dysregulated molecules

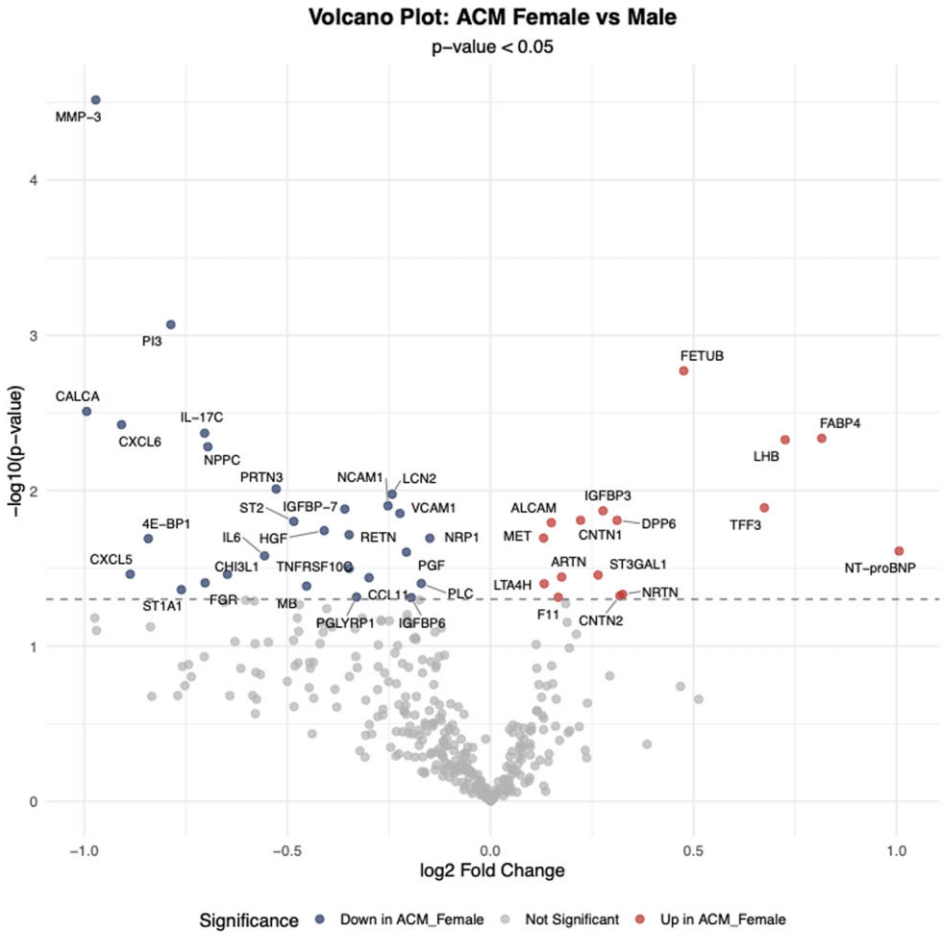

Figure 2. Volcano plot with differential plasma protein expression between women and men with ACM, highlighting proteins significantly higher in women (right) and in men (left) at p<0.05.