

Divergent Responses to Cardiac Resynchronization Therapy: Molecular Profiling Reveals Distinct Fibrotic Gene Expression in Dilated Cardiomyopathy and Ischemic Heart Disease

Sylvia Spiesshofer¹, Bálint András Barta¹, Alex Ali Sayour¹, Albert József Husznai¹, Attila Oláh¹, Mihály Ruppert¹, Dávid Nagy¹, Tímea Bálint¹, Ákos Tóth¹, Béla Merkely¹, Tamás Radovits¹

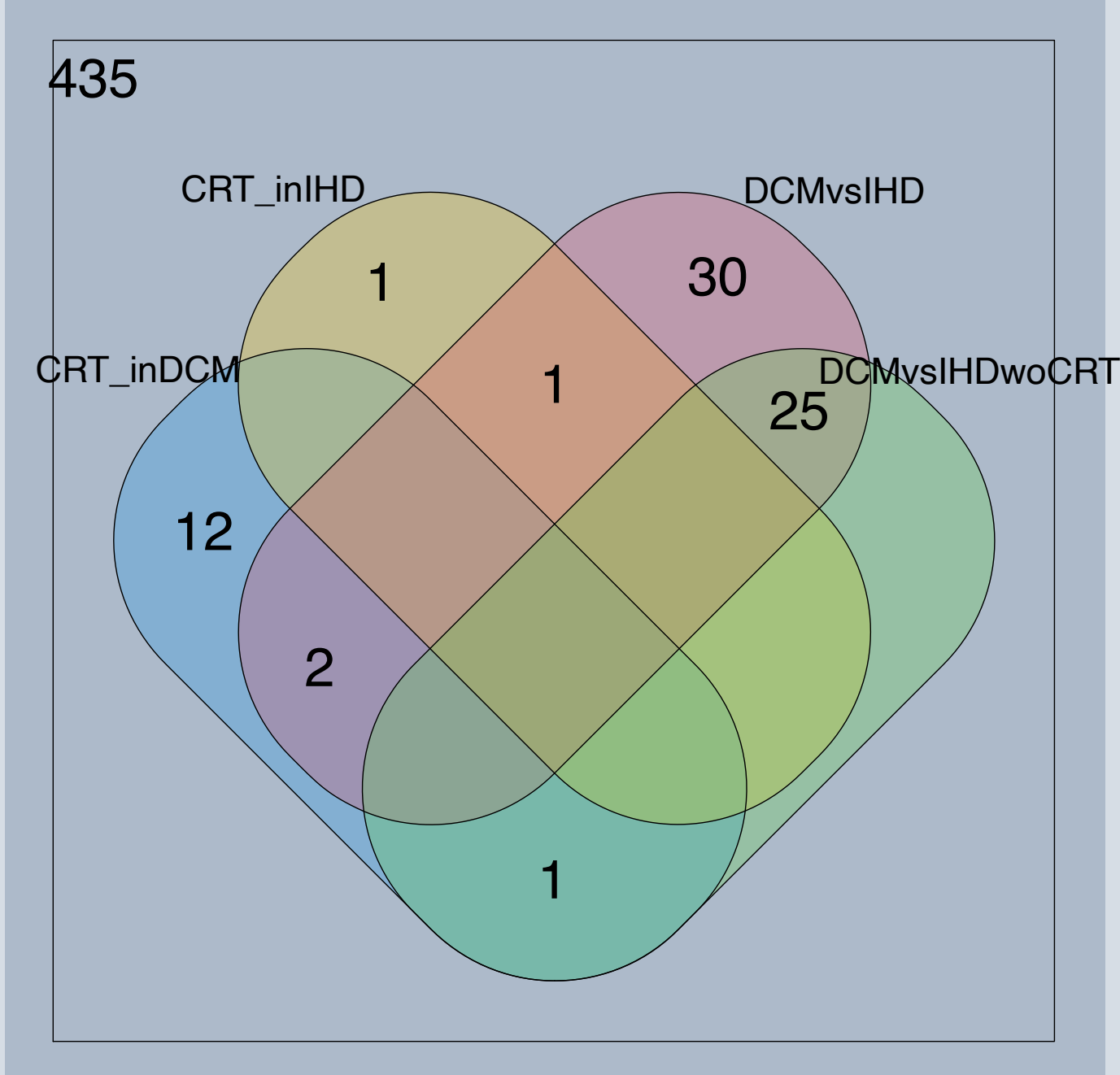
(1) Scientific Research Laboratory, Heart and Vascular Center, Semmelweis University, Budapest, Hungary
Department of Experimental Cardiology and Surgical Techniques, Heart and Vascular Center, Semmelweis University, Budapest, Hungary



Background

Cardiac resynchronization therapy (CRT) improves outcomes in heart failure, yet its molecular effects in different cardiomyopathy subtypes remain poorly understood. Fibrosis, a key driver of disease progression, may underlie variations in CRT responsiveness between dilated cardiomyopathy (DCM) and ischemic heart disease (IHD). This study examines fibrotic gene expression in DCM and IHD, with and without CRT, to identify pathways associated with therapy response.

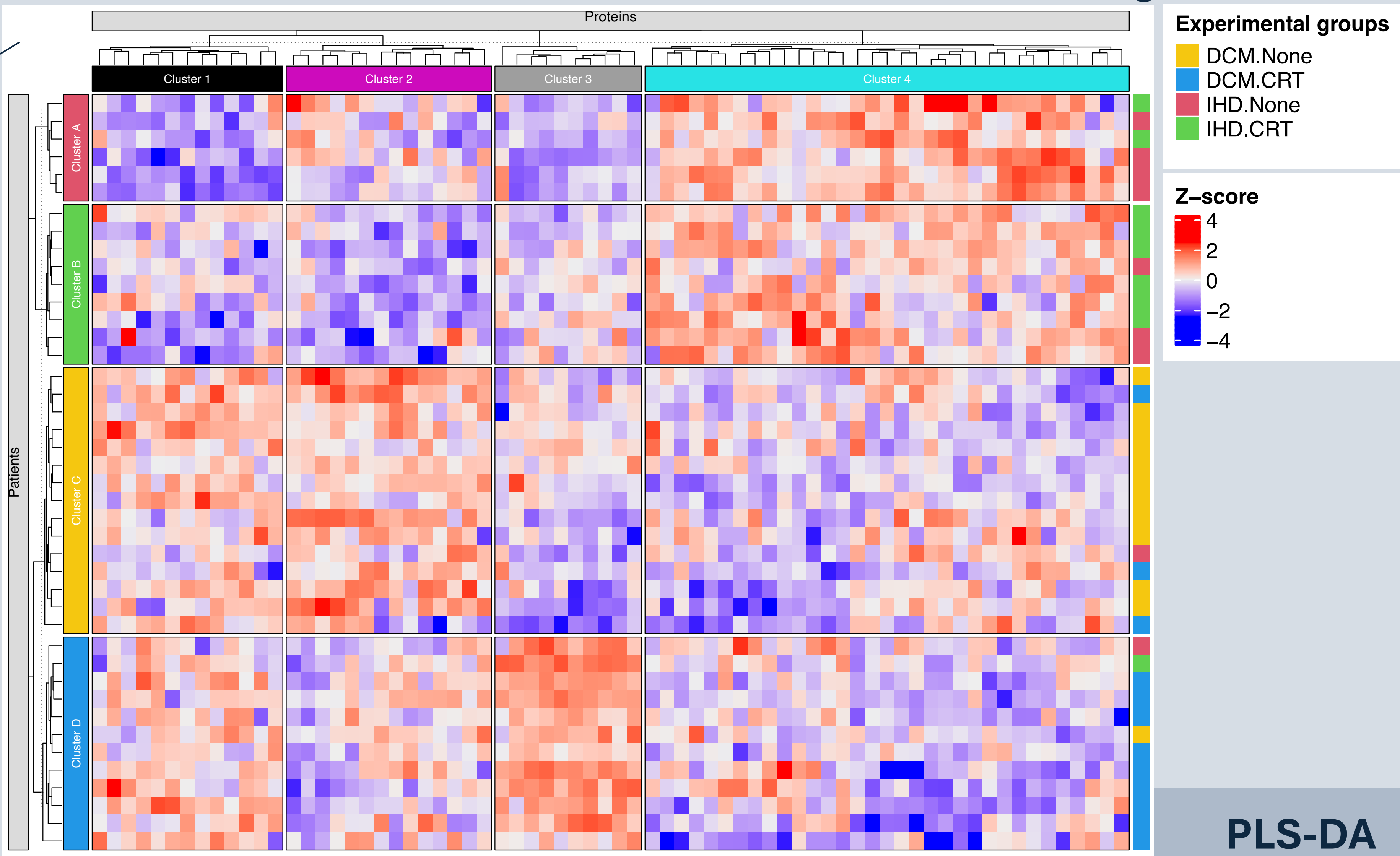
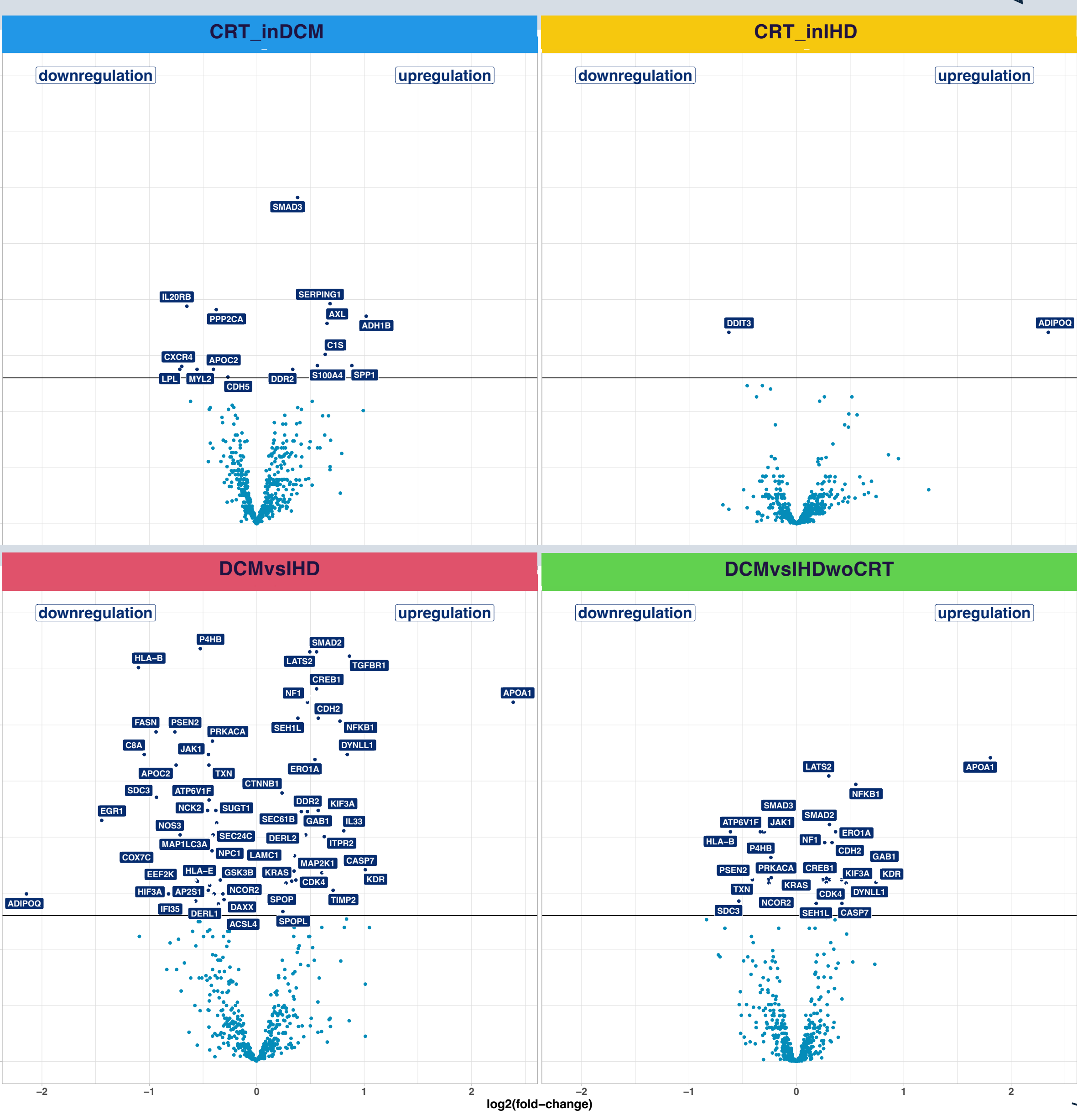
Overlap of Fibrotic Gene Signatures



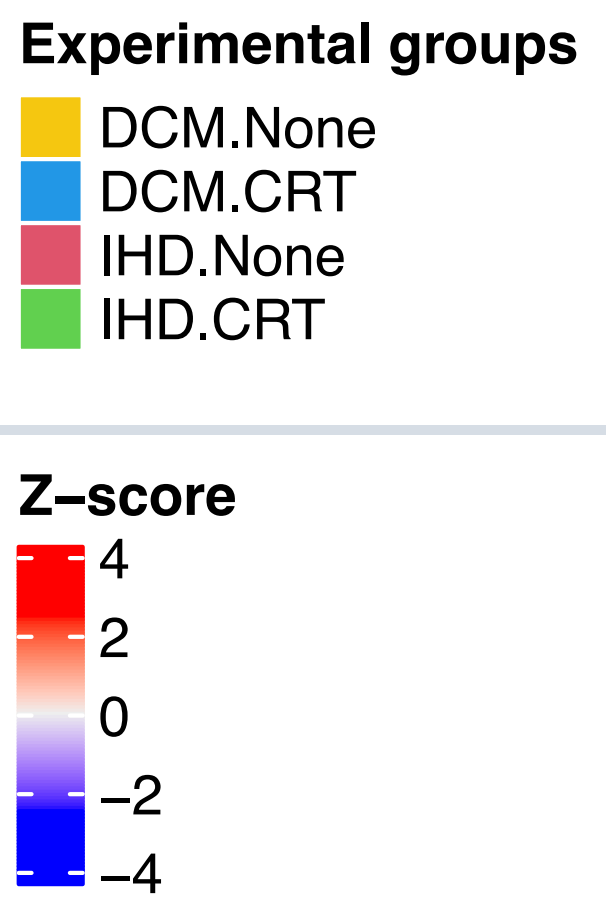
Methods

Snap-frozen myocardial samples were obtained from the transplantation biobank of the Semmelweis University Heart and Vascular Center. Fibrotic remodeling was assessed in DCM and IHD patients using a targeted fibrosis gene panel analyzed via Nanostring technology. The cohort included patients with DCM without CRT (n = 12), DCM with CRT (n = 12), IHD without CRT (n = 9), and IHD with CRT (n = 9). K-means clustering and partial least squares discriminant analysis (PLS-DA) were used to identify molecular patterns distinguishing these groups, and differential expression analysis compared baseline differences and CRT-induced changes.

Differential expression analysis



k-means clustering

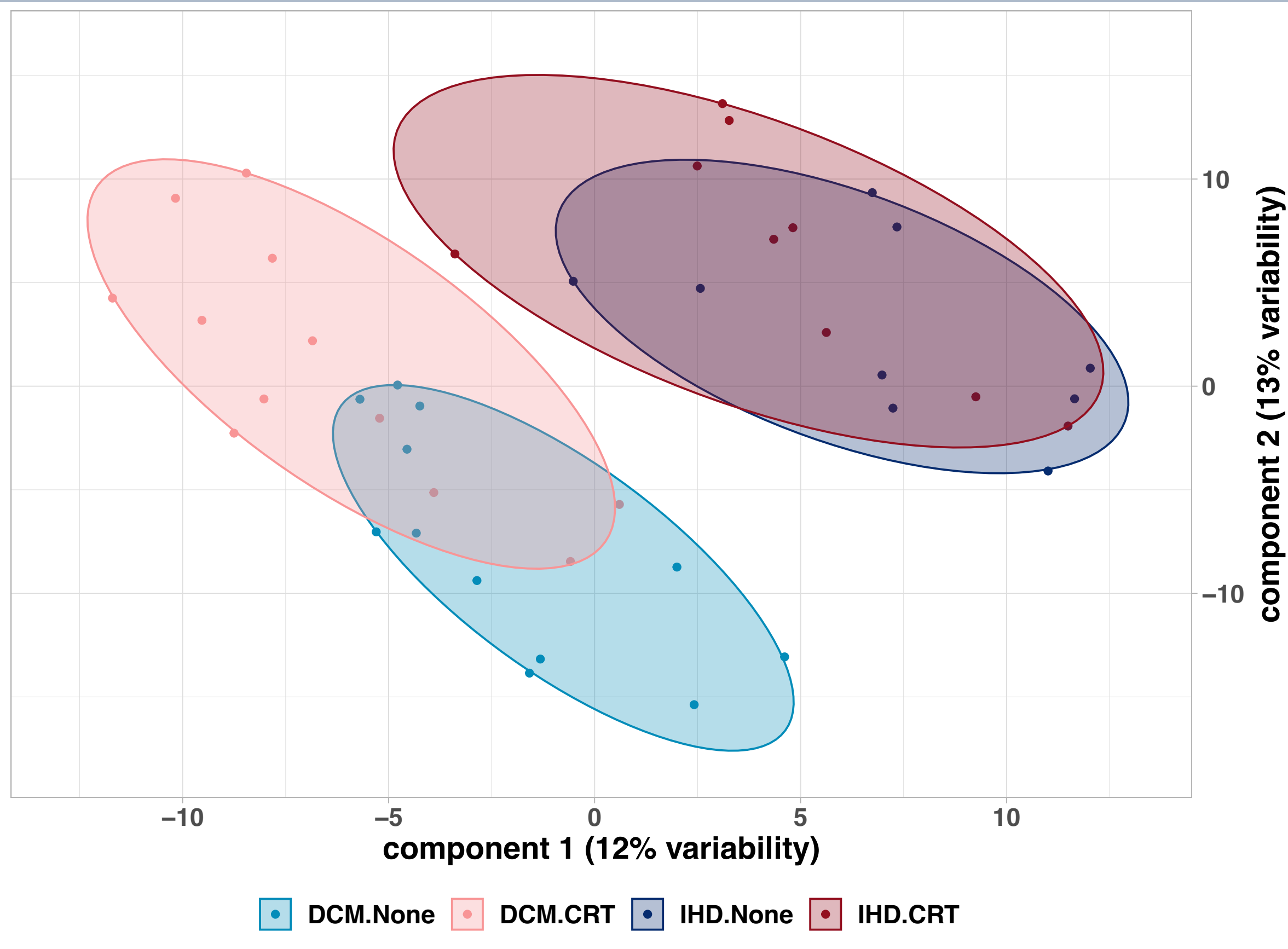


Results

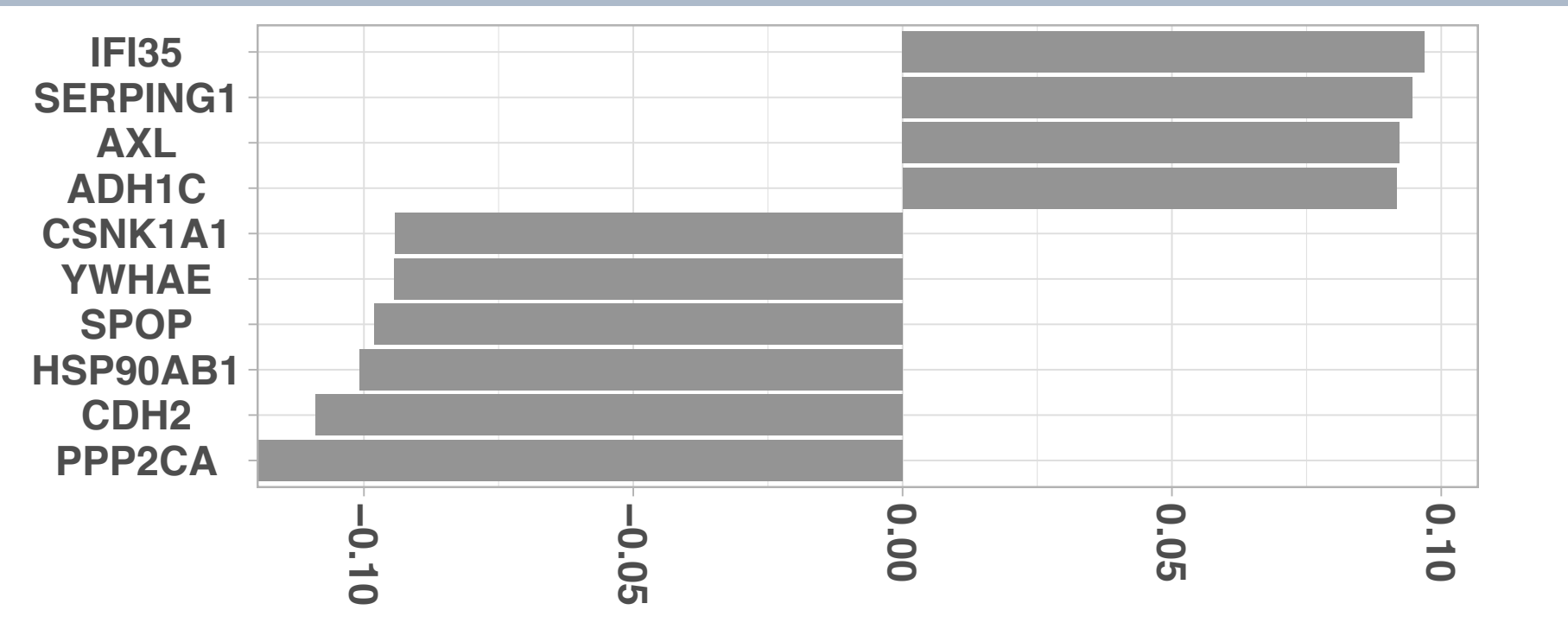
Baseline analysis revealed distinct fibrotic gene expression profiles between DCM and IHD, with SMAD2, NF1, and P4HB, among other genes, upregulated in DCM, indicating a stronger fibrotic signature. CRT induced a robust transcriptional response in DCM, with 15 significantly altered genes, suggesting active reverse remodeling. These include genes regulating fibroblast activation (SERPING1), TGF- β -driven collagen turnover (SMAD3), and tissue repair (AXL). In contrast, IHD showed minimal CRT-induced changes, with only two altered genes (DDIT3, ADIPOQ). PLS-DA demonstrated clear separation between DCM groups based on CRT status, with NF1, SMAD2, and CREB1 driving variability in untreated patients, while P4HB, SDC3, and PRKACA contributing to variability in CRT-treated DCM, indicating enhanced collagen remodeling, fibroblast-ECM interactions, and cAMP-regulated adaptation. IHD groups overlapped substantially, confirming a lack of CRT-driven molecular remodeling. Clustering analysis further reinforced this pattern, with CRT-treated DCM forming a distinct subgroup, while IHD patients remained molecularly similar regardless of CRT status.

Conclusion

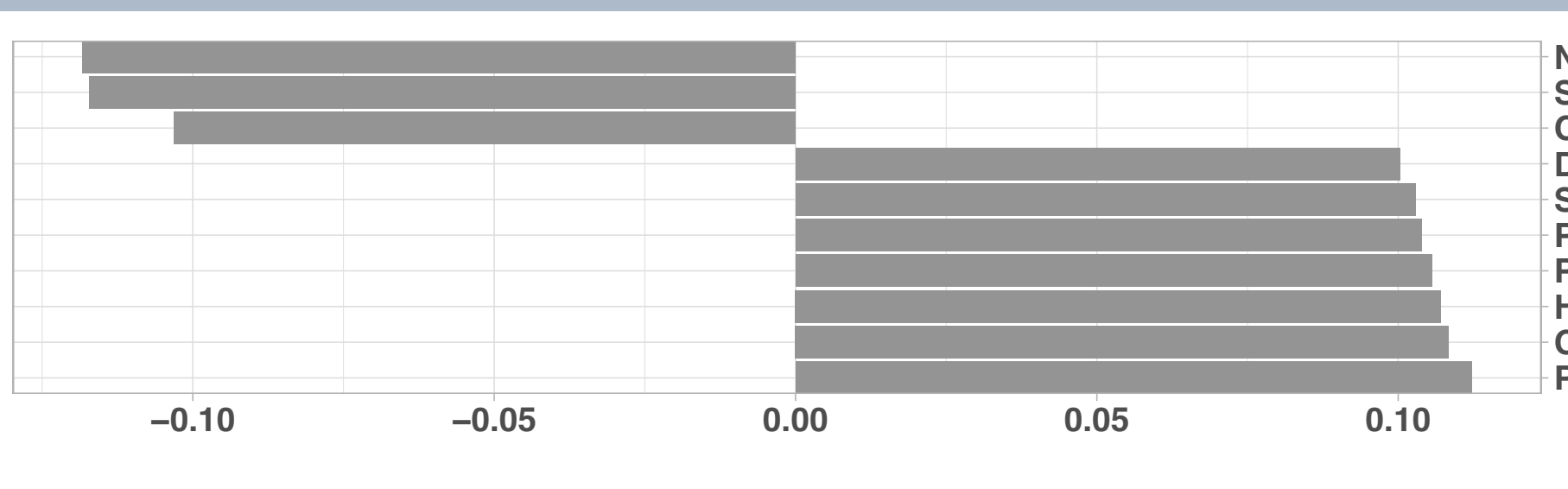
DCM and IHD exhibit distinct baseline fibrotic gene expression and divergent responses to CRT. Identifying key regulators of this process opens the possibility of etiology-specific therapeutic strategies to elicit reverse remodeling.



PLS-DA



Component 2 (13% variability)



Component 1 (12% variability)

Contact: Sylvia Spiesshofer, sylvie.spiesshofer@me.com - Városmajor utca 68, 1122 Budapest, Hungary 📍

Funding: 2022-1.1.1-KK-2022-00005, EKÖP-2024-12, RRF-2.3.1-21-2022-00003, TKP2021-EGA-23, 2024-1.2.3-HU-RIZONT-2024-00059



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