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Supplementary Materials

Candidate Transcriptional Response to Systemic Lupus Erythematosus Immunoglobulin G in Engineered Human Myocardium: An Exploratory Comparison with Non-Lupus Heart Failure

Supplementary Figures

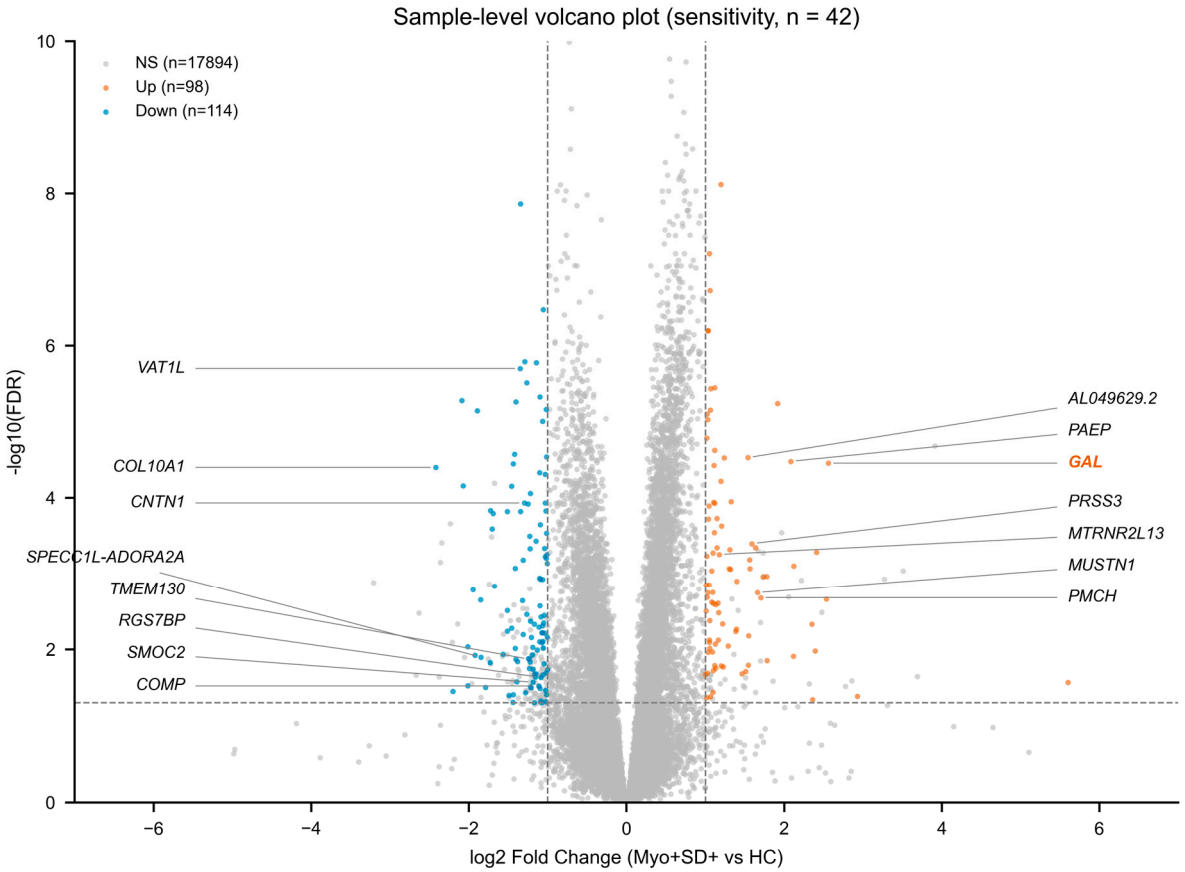

Figure S1. Sample-level differential expression volcano plot. Sample-level volcano plot (Myo+SD+ vs HC; 42 EHM samples, triplicates treated as independent), complementing the donor-level analysis in Fig. 2B. DEGs (FDR < 0.05, |log2FC| > 1): 98 up (orange-red) and 114 down (blue); the 15 candidate program genes are labeled (*GAL* in bold orange-red).

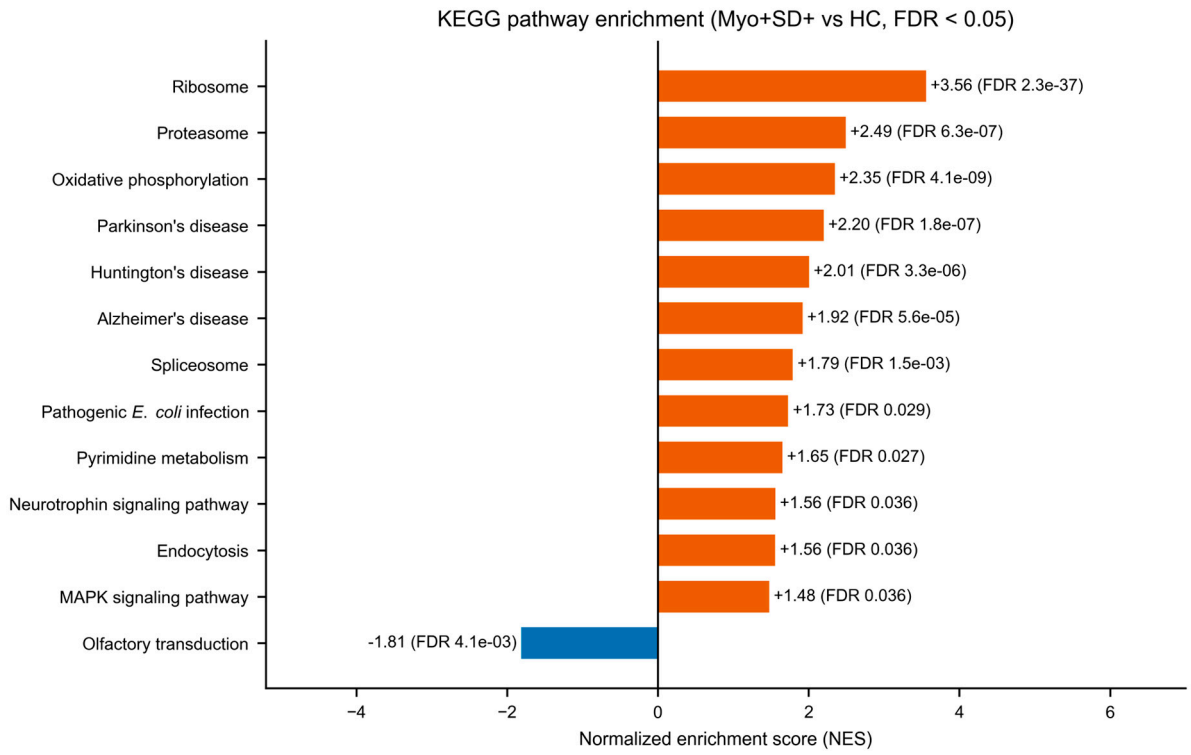

Figure S2. KEGG pathway enrichment in the EHM model. KEGG GSEA results (fgsea v1.38; Wald-statistic gene ranking; Myo+SD+ vs HC). Thirteen pathways reached FDR < 0.05: positive enrichment of the ribosome (NES = +3.56, FDR = 2.3×10^{-37}), proteasome (+2.49, 6.3×10^{-7}), oxidative phosphorylation (+2.35, 4.1×10^{-9}), Parkinson's disease (+2.20, 1.8×10^{-7}), Huntington's disease (+2.01, 3.3×10^{-6}), Alzheimer's disease (+1.92, 5.6×10^{-5}), spliceosome (+1.79, 1.5×10^{-3}), pathogenic E. coli infection (+1.73, 0.029), pyrimidine metabolism (+1.65, 0.027), neurotrophin signaling (+1.56, 0.036), endocytosis (+1.56, 0.036) and MAPK signaling (+1.48, 0.036) pathways, and negative enrichment of olfactory transduction (NES = −1.81, FDR = 4.1×10^{-3}). Enrichment of translation and metabolic pathways should be interpreted cautiously in hiPSC-derived cardiomyocytes, where such signals may partly reflect cellular maturation state or in vitro stress rather than SLE-specific biology.

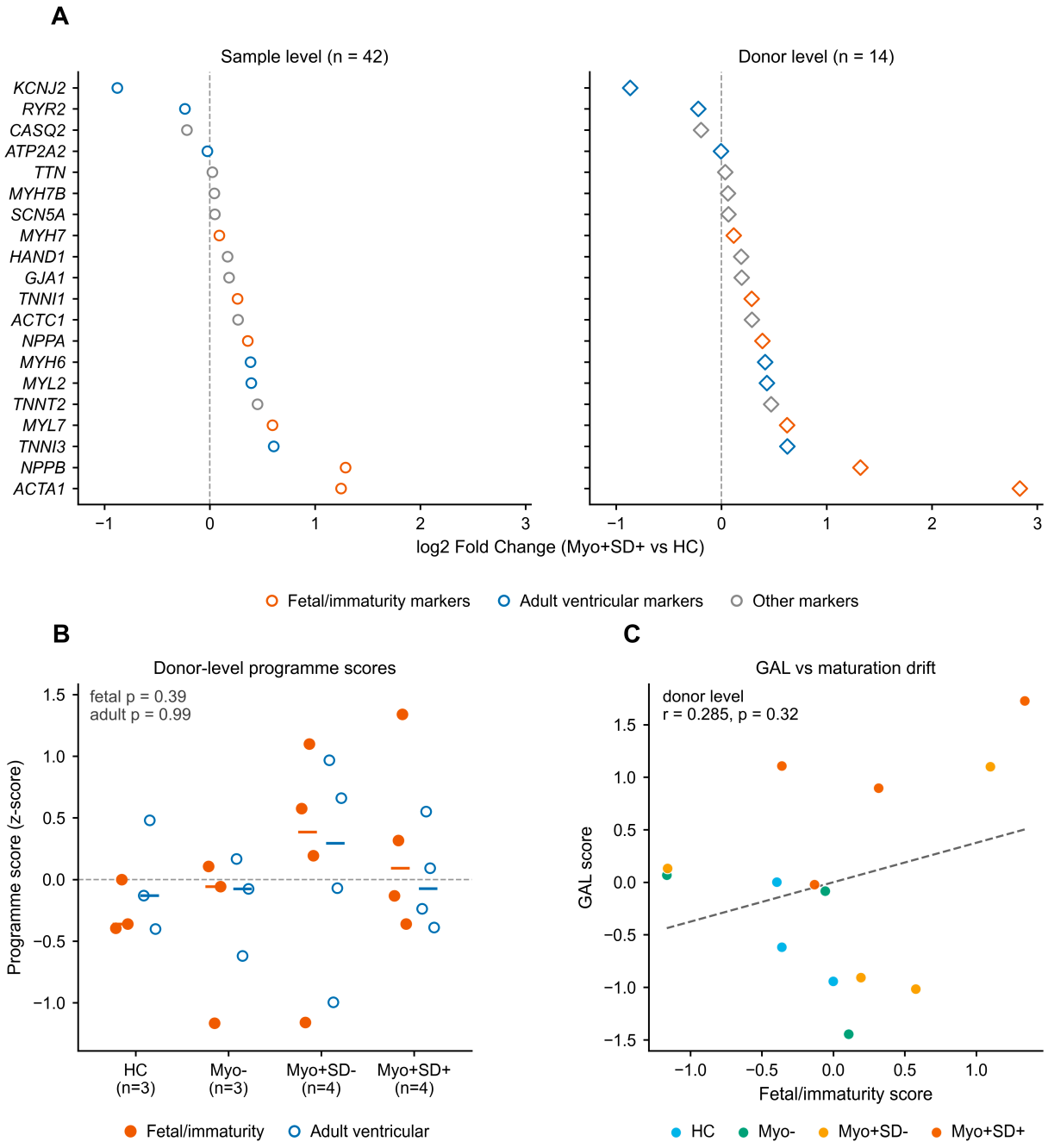

Figure S3. Cardiomyocyte maturation markers in the EHM model. (A) Log2 fold change (Myo+SD+ vs HC) of 20 canonical cardiomyocyte maturation and dedifferentiation markers, displayed in two columns that share the same gene order and the same x-axis scale: sample level (left; open circles; n = 42 samples) and donor level (right; open diamonds; n = 14 donors). Marker edges denote fetal/immature (red), adult ventricular (blue) or other (grey) markers; donor-level diamonds are filled where the donor-level FDR < 0.05, and none reached significance (the donor-level adjusted p-value was not assessable for *ACTA1* owing to independent filtering). The two levels were closely concordant for 19 of the 20 markers ($|\Delta\log2FC| \leq 0.04$); *ACTA1* was the only exception (+1.25 sample level vs +2.83 donor level). (B) Donor-level composite program scores for fetal/immaturity markers

(filled, red; *NPPA*, *NPPB*, *ACTA1*, *MYH7*, *TNNI1*, *MYL7*) and adult ventricular markers (open, blue; *MYH6*, *TNNI3*, *MYL2*, *KCNJ2*, *RYR2*, *ATP2A2*) across the four IgG donor groups; horizontal bars indicate group medians; donor-level Welch p = 0.39 (fetal/immaturity) and p = 0.99 (adult ventricular). In panels A and B, red and blue denote the fetal/immaturity and adult ventricular programs, respectively; donor-group color coding is used only in panel C. (C) Donor-level *GAL* score versus fetal/immaturity program score (n = 14 donors; Pearson r = 0.285, p = 0.32); dashed line is the least-squares fit; point color denotes IgG donor group. These analyses test whether the induction of adult-silent genes reflects a generalized maturation drift of the model; no such coordinated drift was detected, but with 14 donors this represents an absence of evidence rather than evidence of absence.

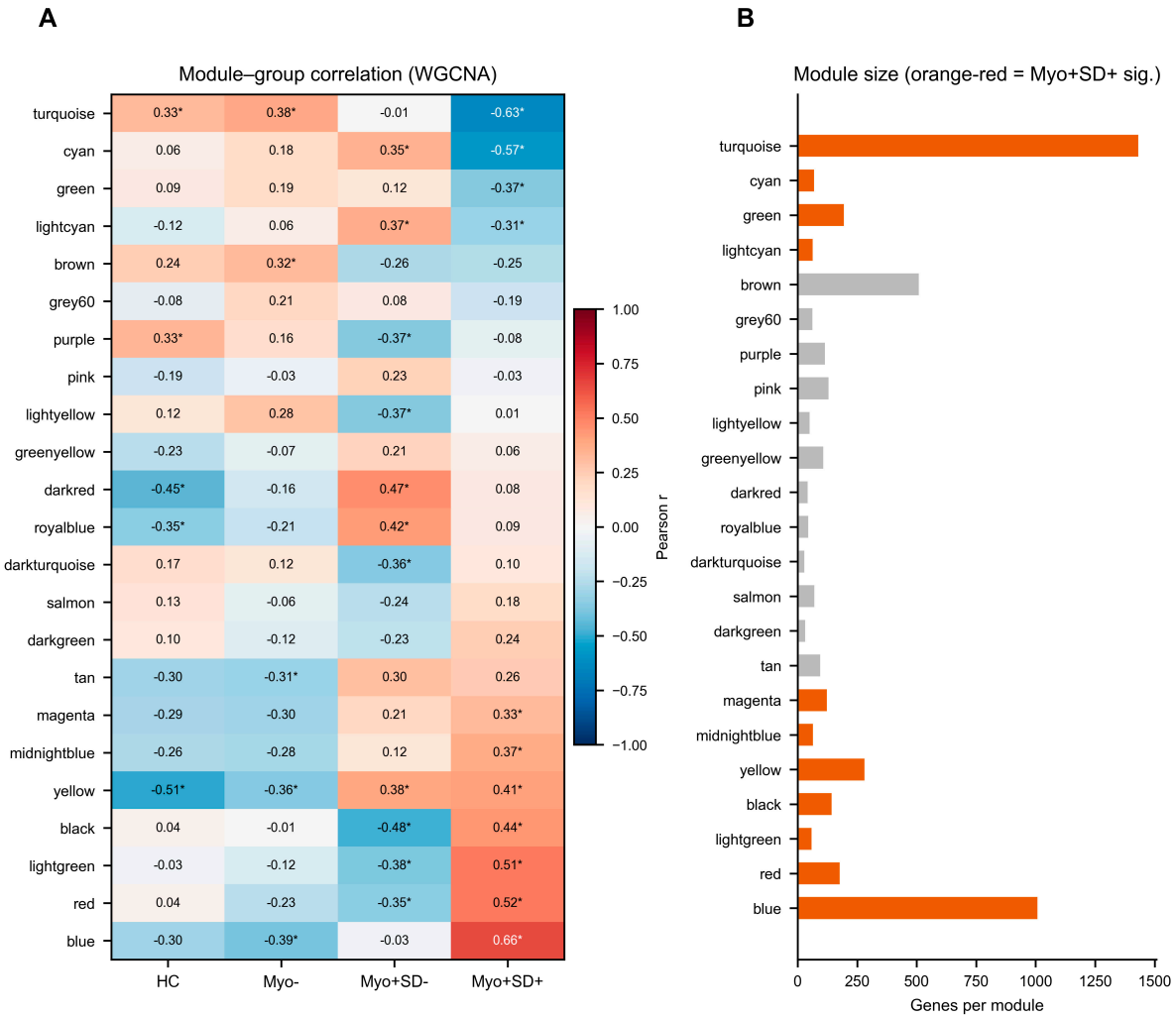

Figure S4. *WGCNA* co-expression modules. (A) Module–group correlation heatmap (23 modules; Pearson correlation of module eigengenes with each clinical group, HC, Myo−, Myo+SD−, Myo+SD+; asterisks denote nominal p < 0.05; modules ordered by correlation with Myo+SD+). (B) Number of genes per module; orange-red bars denote modules with a nominal correlation with the Myo+SD+ group (p < 0.05), of which five (blue, turquoise,

cyan, red and lightgreen) remain significant after Bonferroni correction for 23 modules ($P < 0.00217$).

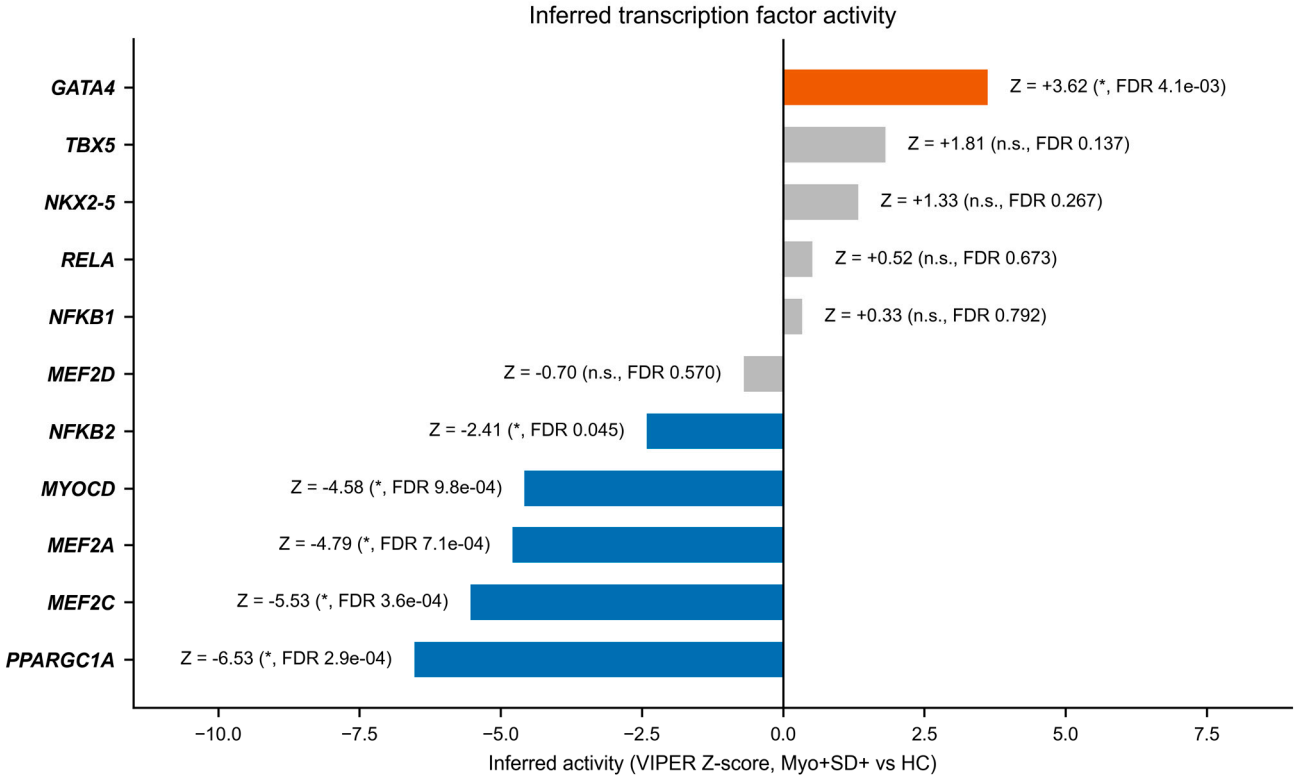

Figure S5. Inferred transcription factor activity (VIPER). Inferred activity changes (Myo+SD+ vs HC) for 11 transcription factors of interest, ranked by VIPER z-score (DoRothEA A–E plus a custom cardiac regulon; 1,333 scorable regulators; see Methods 4.5 for the accounting of the 1,323 DoRothEA regulators plus 10 custom cardiac regulators). Candidate suppression of the cardiac differentiation axis: *PPARGC1A* ($Z = -6.53$, FDR = 2.9×10^{-4}), *MEF2C (–5.53, 3.6 × 10⁻⁴)*, *MEF2A* (−4.79, 7.1×10^{-4}), *MYOCD* (−4.58, 9.8×10^{-4}), and *MEF2D* (−0.70, n.s.); candidate activation of the stress-responsive axis: *GATA4* (+3.62, FDR = 4.1×10^{-3}); NF-κB axis: *NFKB2* (−2.41, FDR = 0.045), *RELA* (+0.52, n.s.), *NFKB1* (+0.33, n.s.). *NKX2-5* (+1.33, n.s.) and *TBX5* (+1.81, n.s.) are shown for context. Asterisks denote FDR < 0.05. Results are computationally inferred regulatory activities, not experimentally validated causal regulators.

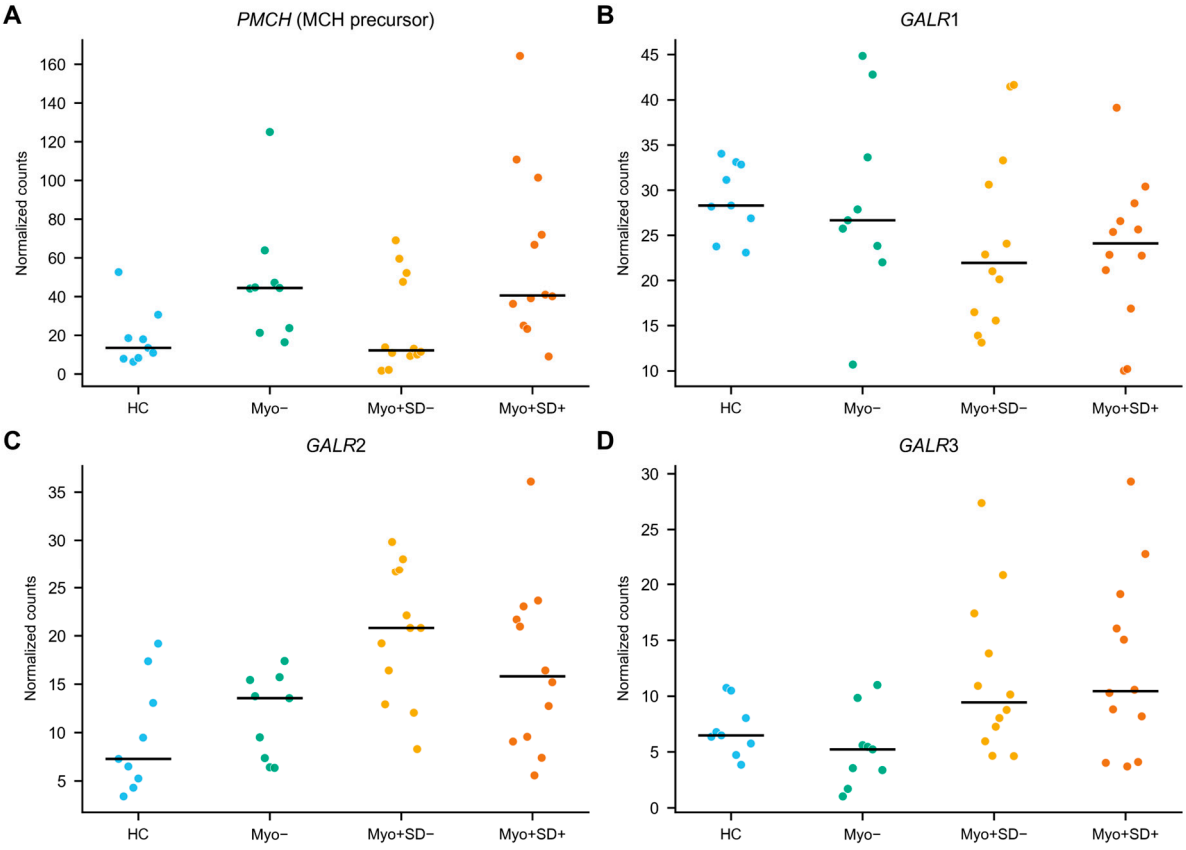

Figure S6. Neuroendocrine gene expression in the EHM model. DESeq2 normalized counts of *PMCH* (A), *GALR1* (B), *GALR2* (C), and *GALR3* (D) across the four groups (42 EHM samples; horizontal bars indicate group medians). *PMCH* is induced in the Myo+SD+ group (≈3.2-fold versus HC); *GALR1–3* are expressed in the model, supporting a neuroendocrine signaling axis in the model. *GAL* expression is shown in Fig. 5A, B.

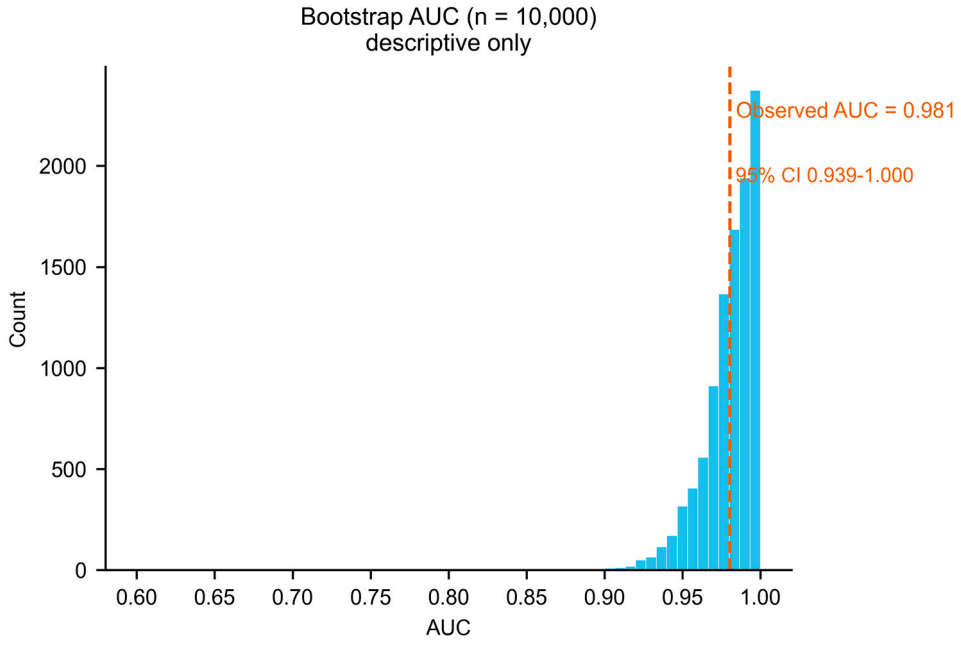

Figure S7. Bootstrap AUC distribution of the locked program score (descriptive only). Histogram of 10,000 bootstrap resamples of the 42 EHM samples; the dashed line marks the observed sample-level AUC of 0.981. The interval plotted here is the tissue-level interval and is shown only to document why it was not retained: resampling tissues treats dependent replicates as independent, and the donor-block alternative (10,000 resamples of the 14 donors within group strata) is degenerate at 1.000 because the 14 donor scores are perfectly separated. No interval is therefore reported in the manuscript. Because feature selection was not repeated within the resampling folds, this distribution describes within-discovery separation of the locked 12-gene scoring core and is not a prospective performance estimate.

Supplementary Tables

Supplementary Table S1. External ssGSEA and Single-Gene Assessment Details

Signed ssGSEA scoring: Score = ssGSEA(upregulated genes) − ssGSEA(downregulated genes), applied to the 15-gene candidate program. Hedges' g for case vs control; random-effects meta-analysis (REML).

1. Signed ssGSEA cohort-level effects

Dataset	Type	n_case	n_ctrl	Hedges' g	SE
GSE50772	SLE peripheral blood	61	20	+0.078	0.2553
GSE61635	SLE peripheral blood	99	30	−1.079	0.2177
GSE72326	SLE peripheral blood	157	20	−0.430	0.2375
GSE65391	SLE peripheral blood	924	72	+0.082	0.1223
GSE116250	Non-SLE HF myocardium	50	14	−0.472	0.3015
GSE57345	Non-SLE HF myocardium	177	136	−1.760	0.1337
GSE42955	HF specificity comparator	12	5	−0.168	0.506

2. Random-effects meta-analysis (signed)

Analysis	k	RE g 95% CI	p	I^2
SLE peripheral blood (GSE50772, GSE61635, GSE72326, GSE65391)	4	−0.33 [−0.87, +0.21]	0.232	87.4%
Non-SLE HF myocardium (GSE116250, GSE57345; primary, k = 2)	2	−1.14 [−2.41, +0.12]	0.075	93.4%
Non-SLE HF myocardium (GSE116250, GSE57345 + comparator GSE42955; sensitivity, k = 3)	3	−0.87 [−1.87, +0.12]	0.085	91.0%

3. Excluded cohorts (with reason)

Dataset	Reason for exclusion
GSE81622	Not in the prespecified meta-analytic set; five-cohort sensitivity in Table S30
GSE141910	Insufficient core-gene detection (RNA-seq data)
GSE303117	HF peripheral blood; evaluated at the individual gene level, not included in the primary meta-analytic framework

4. Unsigned ssGSEA control

Unsigned ssGSEA (all 15 genes treated with equal sign) produced directionally inflated scores in HF myocardium, confirming the methodological rationale for signed scoring when the candidate program contains oppositely directed genes.

Dataset	Unsigned g	Signed g
GSE116250	+1.37	−0.47

5. Platform-detectable sensitivity analysis (12-gene reduced program)

Reduced score = ssGSEA(*GAL*, *PAEP*, *PMCH*, *MUSTN1*, *PRSS3*) − ssGSEA(*VAT1L*, *COL10A1*, *CNTN1*, *TMEM130*, *SMOC2*, *COMP*, *RGS7BP*); protein-coding genes detectable across all platforms (excluding *AL049629.2*, *SPECC1L-ADORA2A*, *MTRNR2L13*).

Dataset	Type	n_case	n_ctrl	Hedges' g	SE
GSE116250	HF myocardium	50	14	−1.828	0.339
GSE57345	HF myocardium	177	136	−1.760	0.134

Meta-analysis (k = 2, HF myocardium, random effects):

Version	RE g	95% CI	p	I^2
Full 15-gene	−1.144	[−2.405, +0.117]	0.0753	93.4%
Reduced 12-gene	−1.769	[−2.013, −1.525]	< 0.0001	0.0%

Interpreted as exploratory only: the reduced formulation also alters gene-set composition (two up-regulated genes removed) and is not presented as a primary positive result.

6. *GAL* single-gene contextual assessment in external cohorts

Dataset	Type	n_case	n_ctrl	Hedges' g	95% CI
GSE116250	HF myocardium (DCM + ICM)	50	14	−0.55	[−1.14, +0.04]
GSE57345	HF myocardium (DCM/ICM)	177	136	−0.62	[−0.85, −0.39]
Random-effects meta-analysis (k = 2)	HF myocardium	—	—	−0.60	[−0.82, −0.40]

GAL single-gene effects in non-SLE HF myocardium (*GAL* expression lower in failing than in non-failing myocardium). Random-effects meta-analysis: g = −0.60 (95% CI −0.82 to −0.40; p < 0.0001; I^2 = 0%). Corresponds to Fig. 5C.

7. *GAL* in SLE peripheral blood (GSE264125; whole blood, RNA-seq)

Comparison	log2FC	p
SLE vs HC (11 vs 10)	+2.00	0.008
CMD vs non-CMD within SLE (4 vs 7)	+2.64	0.003

GSE264125 (SLE whole blood, RNA-seq): sample-level DESeq2 re-analysis of *GAL*. CMD, coronary microvascular dysfunction. This cohort was not part of the 11-dataset ssGSEA screen and was used for *GAL* single-gene contextualization only (Results).

8. Individual-gene-level assessment in non-SLE HF peripheral blood (GSE303117)

Gene	EHM direction	HF mean	Control mean	Hedges' g	95% CI	p (as reported)
PRSS3	Up	0.100	0.070	+0.20	[-0.26, 0.66]	0.281
MUSTN1	Up	0.074	0.157	-0.59	[-1.06, -0.13]	0.042
COL10A1	Down	0.096	0.082	+0.15	[-0.31, 0.61]	0.569
TMEM130	Down	0.032	0.020	+0.16	[-0.30, 0.62]	0.264
COMP	Down	0.028	0.010	+0.25	[-0.21, 0.71]	0.055
GAL	Up	0.012	0.022	-0.13	[-0.59, 0.33]	0.602
VAT1L	Down	0.015	0.005	+0.18	[-0.28, 0.64]	0.124
SMOC2	Down	0.012	0.003	+0.23	[-0.23, 0.69]	0.065
PAEP	Up	0.008	0.000	+0.14	[-0.32, 0.60]	0.199
PMCH	Up	0.008	0.005	+0.07	[-0.39, 0.53]	0.628
AL049629.2	Up	0.007	0.000	+0.13	[-0.33, 0.59]	0.207
SPECC1L-ADORA2A	Down	0.003	0.002	+0.06	[-0.41, 0.52]	0.684
RGS7BP	Down	0.003	0.000	+0.22	[-0.24, 0.68]	0.041
CNTN1	Down	0.002	0.000	+0.14	[-0.32, 0.60]	0.174
MTRNR2L13	Up	0.000	0.000	NA	[NA, NA]	NA

Note: p values in this table are the gene-level p values reported for the source cohort and are not derived from the Hedges' g confidence interval shown alongside them; they are provided for completeness only. Because the two quantities come from different calculations, a confidence interval that includes zero can co-occur with a small reported p (for example *RGS7BP*, g = +0.22 with 95% CI −0.24 to +0.68 and p = 0.041), and effect-size interpretation should rely on g and its interval rather than on the p column. No statement in the main text depends on these p values.

GSE303117 (non-SLE HF peripheral blood, RNA-seq; 107 HF vs 22 controls): single-gene effects for the 15 candidate genes. No consistent directional concordance with the EHM model was observed. This cohort was excluded from the primary meta-analytic framework.

Supplementary Table S2. Tier-1 Threshold Sensitivity and GDMT-Related Pathway Gene Sets.

The nomination is re-run at each threshold (DESeq2 re-fitted with that alpha), and genes retained are counted within the final 15-gene program: 15/15 at the primary threshold (FDR ≤ 0.05, |log2FC| > 1), 2/15 at FDR ≤ 0.01, 2/15 at |log2FC| > 1.5 and 0/15 at |log2FC| > 2.0. Note that re-filtering the primary DESeq2 output at FDR < 0.01 without

re-fitting would retain 6/15; that is a different operation from the re-run reported here. Re-thresholding within the fixed 15-gene set (gene set held constant) is a third operation, reported in Table S21A.

Tier-1 intersection stability under alternative thresholds

Threshold	Genes retained
FDR ≤ 0.1, |log2FC| > 1	15/15
FDR ≤ 0.05, |log2FC| > 1 (primary)	15/15
FDR = 0.01	2/15
|log2FC| > 1.5	2/15
|log2FC| > 2.0	0/15

The Tier-1 intersection (sample-level Myo+SD+ vs HC ∩ Myo+SD+ vs Myo+SD−; 212 ∩ 37) yielded 15 direction-consistent candidate genes and was stable at FDR ≤ 0.1 with |log2FC| > 1 (all 15 genes retained) but contracted under stricter thresholds. Candidate-level donor and sample evidence is provided in Table 1.

GDMT-related pathway gene sets (8 pathways)

Pathway	Genes
Beta-adrenergic / GPCR-cAMP-PKA	*ADRB1*, *ADRB2*, *ADRBK1*, *ADRBK2*, *GNAS*, *GNAI1*, *GNAI2*, *GNAI3*, *ADCY1*, *ADCY2*, *ADCY3*, *ADCY5*, *ADCY6*, *ADCY9*, *PRKACA*, *PRKACB*, *PRKAR1A*, *PRKAR2A*, *CREB1*, *PDE3A*, *PDE4D*, *RYR2*, *PLN*, *ATP2A2*
RAAS / Ang II signaling	*AGT*, *REN*, *ACE*, *ACE2*, *AGTR1*, *AGTR2*, *MAS1*, *NOS3*, *EDN1*, *TGFB1*, *CTGF*, *COL1A1*, *COL3A1*, *CYBB*, *NOX4*, *NFKB1*, *RELA*, *MAPK1*, *MAPK3*
Natriuretic peptide / cGMP	*NPPA*, *NPPB*, *NPR1*, *NPR2*, *NPR3*, *MME*, *GUCY1A1*, *GUCY1B1*, *PRKG1*, *PDE5A*
MR / SGK1 signaling	*NR3C2*, *HSD11B2*, *SGK1*, *SCNN1A*, *SCNN1B*, *SCNN1G*, *NEDD4L*, *TSC22D3*, *FKBP5*, *COL1A1*, *COL3A1*, *TGFB1*
SGLT2i-associated metabolic	*SLC5A2*, *SLC5A1*, *SLC2A1*, *SLC2A4*, *PRKAA1*, *PRKAA2*, *PPARGC1A*, *PPARGC1B*, *SIRT1*, *SIRT3*, *NFE2L2*, *KEAP1*, *TFAM*, *MFN1*, *MFN2*, *OPA1*, *DNM1L*, *PINK1*, *PRKN*, *MAP1LC3B*, *BECN1*, *SQSTM1*, *NLRP3*, *IL1B*, *CASP1*
IFN / JAK-STAT	*IFNAR1*, *IFNAR2*, *JAK1*, *JAK2*, *TYK2*, *STAT1*, *STAT2*, *STAT3*, *IRF1*, *IRF7*, *IRF9*, *ISG15*, *IFIT1*, *IFIT2*, *IFIT3*, *MX1*, *MX2*, *OAS1*, *OAS2*, *OAS3*, *RSAD2*, *DDX58*
GPCR internalization / desensitization	*ARRB1*, *ARRB2*, *ADRBK1*, *ADRBK2*, *CLTC*, *AP2M1*, *DNM1*, *DNM2*, *RAB5A*, *RAB7A*, *RAB11A*, *CAV1*, *CAV2*, *SRC*, *GRK5*, *GRK6*
Calcium handling	*RYR2*, *ATP2A2*, *PLN*, *CASQ2*, *CACNA1C*, *SLC8A1*, *CAMK2D*, *PPP1R1A*, *TRDN*, *JPH2*

Curated from MSigDB and the literature; used for GSVA pathway scoring (GSVA v2.6.2) across the 42 EHM samples; correlation results in Supplementary Table S7.

Supplementary Table S3. Differential Expression Results for the Primary Comparisons

Provided as a separate supplementary file in this submission: TableS3_Full_DEG_results.csv (144,848 data rows plus header; also deposited in the code archive, results/TableS3_Full_DEG_results.csv)

Columns: baseMean, log2FoldChange, lfcSE, stat, pvalue, padj, gene, sig, Contrast, Significant. All four primary contrasts are included (Myo+SD+ vs HC, Myo+SD+ vs Myo+SD−, Myo+SD− vs HC and Myo− vs HC), each at the donor (pseudobulk, n = 14) and sample (n = 42) levels.

Supplementary Table S4. Overlap with Inflammatory Gene Sets.

Gene set	N genes	N overlap	Jaccard	Expected overlap (hypergeometric)	P(no overlap)
NF-κB targets	31	0	0	0.026	0.975
IFN-α pathway	19	0	0	0.016	0.984
TNF-α signaling	20	0	0	0.017	0.984
Inflammatory response	29	0	0	0.024	0.976
Cardiac hypertrophy	30	0	0	0.025	0.975

Overlap between the 15-gene candidate program and five curated inflammatory/stress sets (NF-κB targets, IFN-α pathway, TNF-α signaling, inflammatory response and cardiac hypertrophy; 19–31 genes each). For each set the table gives the Jaccard index, the hypergeometric expected overlap and P(no overlap); n = 15 program genes. No multiplicity correction was applied to this descriptive comparison.

Supplementary Table S5. Program scores by sample and nested leave-one-donor-out cross-validation results

Cross-validated performance of the two procedures. Locked 12-gene score: TP 4 / FN 0 / FP 5 / TN 5, accuracy 9/14 (64.3%), sensitivity 1.00, specificity 0.50, balanced accuracy 0.750. Nested selection (feature selection repeated within each training fold): TP 4 / FN 0 / FP 7 / TN 3, accuracy 7/14 (50.0%), sensitivity 1.00, specificity 0.30, balanced accuracy 0.650. The no-information rate is 10/14 (71.4%).

Sample	Group	Score
GS004	HC	0.1010
GS005	HC	−0.6878
GS006	HC	−0.1873
GS007	HC	−0.8232

Sample	Group	Score
GS008	HC	−0.8666
GS009	HC	−0.9154
GS010	HC	−0.5967
GS011	HC	−0.2564
GS012	HC	−0.3777
GS013	Myo−	−0.5090
GS014	Myo−	−0.4971
GS015	Myo−	−0.3792
GS016	Myo−	−0.1728
GS017	Myo−	−0.0311
GS018	Myo−	−0.4702
GS019	Myo−	−0.0527
GS020	Myo−	−0.3113
GS021	Myo−	0.0419
GS022	Myo+SD-	−0.8784
GS023	Myo+SD-	−0.5448
GS024	Myo+SD-	−0.7581
GS025	Myo+SD-	−0.7364
GS026	Myo+SD-	0.1058
GS027	Myo+SD-	−0.1314
GS028	Myo+SD-	0.7224
GS029	Myo+SD-	0.3578
GS030	Myo+SD-	0.3049
GS031	Myo+SD-	−0.8504
GS032	Myo+SD-	−0.1245
GS033	Myo+SD-	−0.2833
GS034	Myo+SD+	0.2663
GS035	Myo+SD+	0.5419
GS036	Myo+SD+	0.7736
GS037	Myo+SD+	0.9471
GS038	Myo+SD+	0.6125
GS039	Myo+SD+	1.4033
GS040	Myo+SD+	0.7965
GS041	Myo+SD+	1.2417

Sample	Group	Score
GS042	Myo+SD+	1.0028
GS043	Myo+SD+	0.9520
GS044	Myo+SD+	0.3469
GS045	Myo+SD+	0.9234

Program scores were computed as the directionally weighted mean of z-scores across 12 of the 15 program genes (*COMP*, *SMOC2* and *TMEM130* excluded), z-standardized on log2-transformed DESeq2 normalized counts across the 42 EHM samples. Sample-level leave-one-out cross-validation with fold-wise Youden thresholds correctly classified 38 of 42 samples (90.5%).

Nested leave-one-donor-out CV (feature selection repeated within each fold)

Feature selection was repeated within each leave-one-donor-out fold; the selected gene set varied across folds (2–69 genes; 128 distinct genes in total, no gene selected in all 14 folds, median pairwise Jaccard 0.25), and overall accuracy was 7/14 (50.0%).

Held-out donor	Group	n_features selected	Correct
1	HC	14	No
2	HC	8	Yes
3	HC	13	No
4	Myo−	13	No
5	Myo−	15	Yes
6	Myo−	12	No
7	Myo+SD−	6	Yes
8	Myo+SD−	6	No
9	Myo+SD−	61	No
10	Myo+SD−	12	No
11	Myo+SD+	69	Yes
12	Myo+SD+	2	Yes
13	Myo+SD+	32	Yes
14	Myo+SD+	12	Yes

Supplementary Table S6. Sample Metadata (GSE227571; 42 EHM samples)

Sample	Group	IgG donor
GS004	HC	1

GS005	HC	1
GS006	HC	1
GS007	HC	2
GS008	HC	2
GS009	HC	2
GS010	HC	3
GS011	HC	3
GS012	HC	3
GS034	Myo+SD+	11
GS035	Myo+SD+	11
GS036	Myo+SD+	11
GS037	Myo+SD+	12
GS038	Myo+SD+	12
GS039	Myo+SD+	12
GS040	Myo+SD+	13
GS041	Myo+SD+	13
GS042	Myo+SD+	13
GS043	Myo+SD+	14
GS044	Myo+SD+	14
GS045	Myo+SD+	14
GS022	Myo+SD-	7
GS023	Myo+SD-	7
GS024	Myo+SD-	7
GS025	Myo+SD-	8
GS026	Myo+SD-	8
GS027	Myo+SD-	8
GS028	Myo+SD-	9
GS029	Myo+SD-	9
GS030	Myo+SD-	9

GS031	Myo+SD-	10
GS032	Myo+SD-	10
GS033	Myo+SD-	10
GS013	Myo−	4
GS014	Myo−	4
GS015	Myo−	4
GS016	Myo−	5
GS017	Myo−	5
GS018	Myo−	5
GS019	Myo−	6
GS020	Myo−	6
GS021	Myo−	6

Total: 42 EHM RNA-seq samples from 14 IgG donors (three EHM tissue replicates per donor). Groups: HC (n = 9 samples, 3 donors), Myo− (n = 9, 3), Myo+SD− (n = 12, 4), Myo+SD+ (n = 12, 4). Myocardial inflammation assessed by ^{18}F-FDG PET/CT; systolic dysfunction defined as EF < 50%. Cohort-level summary in Table 2.

Supplementary Table S7. GDMT Pathway Correlations

Pathway	Spearman ϱ	P-value	FDR	Sig.
MR SGK1	-0.366	0.0177	0.0283	Yes
Natriuretic cGMP	-0.665	3.1e-06	1.24e-05	Yes
Beta adrenergic	-0.687	1.24e-06	9.92e-06	Yes
GPCR internalization	0.418	0.00631	0.0126	Yes
RAAS	0.005	0.977	0.977	No
SGLT2i Metabolic	-0.626	1.46e-05	3.89e-05	Yes
Ca handling	-0.264	0.0918	0.122	No
IFN JAK STAT	-0.147	0.35	0.4	No

Note: pathway scores (ssGSEA, GSVA v2.6.2) were computed on the 42 EHM samples with the gene sets listed in Supplementary Table S2 and correlated (Spearman) with the 12-gene scoring core program score. Benjamini–Hochberg correction across the eight

pathways. The donor-level counterpart, computed with the same gene sets on donor pseudobulk profiles (n = 14), is given in Supplementary Table S16; the sample-level and donor-level analyses now use identical pathway definitions and the same dependent variable.

Supplementary Table S8. WGCNA Co-expression Module Results

Weighted gene co-expression network analysis (WGCNA; signed network, soft-threshold power selected by scale-free fit, TOM-based hierarchical clustering with dynamic tree cut; 5,000 genes subsampled at random with seed 42). Module–trait correlations are Pearson correlations between module eigengenes and the Myo+SD+ indicator across 42 EHM samples (P-values unadjusted; * P < 0.05). Full gene-to-module assignment is provided as TableS8_WGCNA_gene_module_mapping.csv (5,000 genes).

Module summary and association with Myo+SD+

Module	Genes	r (Myo+SD+)	P	Representative hub genes
turquoise	1436	−0.634*	6.44e-06	*NEDD9*, *RPS6KB1*, *IFIT2*, *AC009690*.1
blue	1012	0.655*	2.52e-06	*TSR3*, *APRT*, *PQBP1*, C7orf50
brown	514	−0.252	1.08e-01	*TDGF1*, *CLOCK*, *PPP4R1*, *MAPK8*
yellow	285	0.409*	7.10e-03	*LRFN4*, *SLC39A13*, *PGS1*, *VPS37B*
green	199	−0.372*	1.53e-02	*TRIM22*, *ACTG2*, *TAL1*, *PCDHB7*
red	181	0.516*	4.74e-04	*GNPDA1*, *ECHS1*, *MT-CO1*, *CATIP*
black	147	0.444*	3.20e-03	*EIF5B*, *EIF1AX*, *TAF11*, *EID3*
pink	134	−0.029	8.54e-01	*SYT7*, *CEBPA*, *LRRC52*, *ATG9B*
magenta	127	0.326*	3.50e-02	*TEX264*, *PIGZ*, *JMY*, *HIST2H2AA4*
purple	119	−0.077	6.28e-01	*IL15*, *PSPHP1*, *CDCA7*, *CCDC110*
greenyellow	112	0.060	7.07e-01	*AC073264*.3, *BACE2*, *TNFSF9*, *HDLBP*
tan	99	0.258	9.94e-02	*ACTA1*, *PLA1A*, *HSPB2*, *PCSK7*
salmon	75	0.182	2.49e-01	*REC8*, *GBP1P1*, *KIF26B*, *IGFLR1*
cyan	73	−0.570*	8.04e-05	*ZSCAN25*, *KDM5D*, *TPP1*, *VPS52*
midnightblue	69	0.372*	1.52e-02	*LRRC4B*, *EVA1B*, *SUMF2*, *HRH1*
lightcyan	68	−0.310*	4.55e-02	*HIRA*, *BAZ2A*, *AFAP1L2*, *SPRY2*
grey60	67	−0.191	2.27e-01	*ADAM28*, *GJB1*, *A1CF*, *ARL14*
lightgreen	63	0.513*	5.18e-04	*MRPS6*, *TMEM242*, *GTF2IRD2*, *PET117*
lightyellow	55	0.008	9.62e-01	*RAB9A*, *AKAP9*, *STARD3NL*, *RRN3P1*
royalblue	49	0.091	5.67e-01	*PREX1*, *CAND2*, *TBC1D24*, *APBA2*
darkred	47	0.085	5.94e-01	*MAML1*, *NKD2*, *KCTD5*, *FLNB*
darkgreen	36	0.243	1.21e-01	*TACC3*, *BTN3A2*, *SNX32*, *UBE2C*

Module	Genes	r (Myo+SD+)	P	Representative hub genes
darkturquoise	33	0.097	5.40e-01	*ERLEC1*, *MTF2*, *DDX18*, *GPR89A*

Key findings: the turquoise module (n = 1,436 genes; the largest) was significantly negatively correlated with the Myo+SD+ phenotype ($r = -0.634$, $P = 6.4 \times 10^{-6}$), and the blue module (n = 1,012) was significantly positively correlated ($r = +0.655$, $P = 2.5 \times 10^{-6}$), indicating coordinated transcriptional reorganization associated with severe cardiac involvement.

Supplementary Table S9. Immune pathway association with the candidate program score

Pathway	N genes detected	Spearman ρ	FDR	Gene set used
TGFβ signaling	14/16	-0.542	0.00211	*TGFB1, TGFB2, TGFB3, TGFBR1, TGFBR2, SMAD2, SMAD3, SMAD4, SMAD7, SERPINE1, CTGF, TAGLN, ACTA2, COL1A1, FN1, CDH2*
Chemokine signaling	13/22	0.46	0.0096	*CCL2*, *CCL3*, *CCL4*, *CCL5*, *CCL7*, *CCL8*, *CCL13*, *CCL20*, *CXCL1*, *CXCL2*, *CXCL8*, *CXCL9*, *CXCL10*, *CXCL11*, *CXCL16*, *CCR1*, *CCR2*, *CCR5*, *CCR7*, *CXCR3*, *CXCR4*, *CX3CR1*
Complement	17/20	-0.24	0.202	*C1QA, C1QB, C1QC, C2, C3, C4A, C4B, C5, CFB, CFD, CFH, CFI, SERPING1, C1R, C1S, MASP1, MASP2, CD55, CD59, CD46*
Antigen presentation	17/19	0.386	0.0323	*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DMA*, *HLA-DMB*, *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DRA*, *HLA-DRB1*, *B2M*, *TAP1*, *TAP2*, *TAPBP*, *PSMB8*, *PSMB9*, *CD74*, *CIITA*
Fc receptor	2/7	0.192	0.293	*FCGR1A*, *FCGR1B*, *FCGR2A*, *FCGR2B*, *FCGR2C*, *FCGR3A*, *FCGR3B*
IL-1 / Inflammasome	12/13	0.179	0.293	*IL1A, IL1B, IL18, NLRP3, NLRC4, AIM2, PYCARD, CASP1, IL1R1, IL1RAP, MYD88, IRAK1, IRAK4*
TNF / NF-κB	13/14	0.252	0.202	TNF, TNFRSF1A, TNFRSF1B, TNFAIP3, NFKB1, RELA, NFKB2, RELB, TRAF2, TRAF6, RIPK1, IKBKB, IKBKG, CHUK
Interferon	20/20	-0.003	0.985	*IFIT1*, *IFIT2*, *IFIT3*, *IFI44*, *IFI44L*, *IFIH1*, *MX1*, *MX2*, *OAS1*, *OAS2*, *OAS3*, *OASL*, *ISG15*, *STAT1*, *STAT2*, *IRF1*, *IRF3*, *IRF7*, *IRF9*, *DDX58*

Note: pathway scores (ssGSEA) were computed on the 42 EHM samples and correlated (Spearman) with the 12-gene scoring core program score, with Benjamini–Hochberg correction across the eight pathways. The same eight gene sets (members listed in the right-hand column) are used for the donor-level analysis in Supplementary Table S16, so the two levels are directly comparable. Effect sizes are modest and the analysis is exploratory: it describes co-variation between pathway activity and the candidate program within one in vitro dataset, and does not establish pathway activity in SLE-HF myocardium. Member-gene associations, including genes moving in the direction opposite to their pathway score, are reported in Supplementary Table S23.

Supplementary Table S10. Scoring-Core Sensitivity Analysis (12-Gene Core versus All 15 Candidate Genes)

Note on metrics: the AUC values in this table are descriptive summaries of within-discovery separation (bootstrap, 10,000 iterations) and are not performance estimates. The cross-validated accuracy in Table S18 is a 42-sample metric computed with donor-held-out thresholds; it is not the donor-level leave-one-donor-out accuracy reported in Results 2.3 (9/14 for the 12-gene core, 10/14 for the full 15-gene panel). The two tables therefore report different quantities. Donor-level values for all five gene sets, with exact, bootstrap and Wilson intervals, are given in Supplementary Table S26.

Internal robustness metrics for the locked program score computed with the 12-gene scoring core (main analysis) and with all 15 candidate genes (sensitivity analysis). The score is the directionally weighted mean z-score of log2(normalized count + 1); z-score parameters were estimated once across all 42 EHM samples and kept fixed; donor-level scores are the mean of the three replicate scores per donor; the leave-one-donor-out classification threshold is the median score of the non-Myo+SD+ training donors. AUC = area under the receiver operating characteristic curve; CI = confidence interval; LOOCV = leave-one-out cross-validation. The locked-score bootstrap AUC referred to in Results 2.3 is reported here as a descriptive statistic only: observed AUC = 0.981 (Supplementary Figure S7); no interval is reported, for the reason given in Methods 4.7; the same bootstrap procedure applied to the 15-gene and 7-gene variants gave 0.978 and 0.983. AUC is not used as a performance estimate; donor-level cross-validated accuracy against the no-information rate is the primary read-out. The tissue-level bootstrap interval is no longer reported: resampling the 42 tissues treats dependent replicates as independent, and the donor-block alternative is degenerate at 1.000 because the 14 donor scores are perfectly separated (Methods 4.7). The 9/14 donor-level accuracy given here for the 15-gene panel

fixes the z-score parameters across all 42 samples; when they are re-estimated inside each training fold, as in Supplementary Table S26, the same panel gives 10/14, and the two values therefore describe the same procedure under two normalization conventions rather than disagreeing.

Metric	12-gene core	All 15 candidate genes
Scoring core, n genes	12	15
Sample-level AUC	0.9806	0.9778
Sample-level LOOCV, Youden (n = 42)	38/42 (90.5%)	39/42 (92.9%)
Donor-level AUC (in-sample, n = 14)	1.000	1.000
Leave-one-donor-out accuracy	9/14 (64.3%)	9/14 (64.3%)
Donor-level permutation p (C(14,4) = 1,001)	0.0010	0.0010
Correlation with the alternative score (sample level)	r = 0.974	r = 0.974
Correlation with the alternative score (donor level)	r = 0.982	r = 0.982

Supplementary Table S11. Donor-Level Significance of the 15 Program Genes under Two Preprocessing Variants (Myo+SD+ vs HC)

Donor-level DESeq2 results (n = 14 donors). The primary pipeline reports adjusted p-values after DESeq2 independent filtering, in which low-mean-count genes receive no adjusted p-value (the gene-wise test is performed, but DESeq2 independent filtering sets the adjusted value to NA); five program genes (*PAEP*, *PMCH*, *MUSTN1*, *MTRNR2L13*, *RGS7BP*) fall below the filter and therefore contribute to the conservative primary count of 7 donor-level significant genes. The alternative variant retains those genes, so that 10 of 15 genes reach donor-level FDR < 0.05. Log2 fold changes are identical between the two variants; only the adjusted p-values differ. The conservative count of 7 is used throughout the main text.

Gene	Donor log2FC	padj (primary)	padj (alternative)	Significant (primary)	(pri-Significant (alternative)
GAL	2.528	0.0273	0.0306	Yes	Yes
PAEP	2.055	NA	0.0136	No	Yes
AL049629.2	1.524	0.0087	0.0097	Yes	Yes
PMCH	1.658	NA	0.0426	No	Yes
MUSTN1	1.673	NA	0.2030	No	No

PRSS3	1.548	0.0095	0.0107	Yes	Yes
MTRNR2L13	1.171	NA	0.0274	No	Yes
VAT1L	−1.329	6.81e-04	7.51e-04	Yes	Yes
COL10A1	−2.457	0.0154	0.0173	Yes	Yes
CNTN1	−1.266	0.0112	0.0126	Yes	Yes
SPECC1L-ADORA2A	−1.837	3.51e-07	3.72e-07	Yes	Yes
TMEM130	−1.244	0.1499	0.1628	No	No
SMOC2	−1.183	0.1651	0.1790	No	No
COMP	−1.122	0.1665	0.1804	No	No
RGS7BP	−1.081	NA	0.0837	No	No

Supplementary Table S12. External immaturity check: expression of the 15 program genes in iPSC-derived cardiomyocytes, undifferentiated iPSC, fetal heart and adult heart (GSE154580)

Mean expression (RPM) of each program gene in an independent, uniformly processed public dataset (GSE154580) containing human iPSC-derived cardiomyocytes (n = 3), undifferentiated human iPSC (n = 3), human fetal heart (n = 1) and adult human heart / left ventricle (n = 3). Of the up-regulated arm, *GAL*, *PAEP* and *PMCH* are barely detectable in iPSC-derived cardiomyocytes and fetal heart, whereas *PRSS3* is higher in fetal than in adult heart (6.97 vs 0.15 RPM) and *MUSTN1* is adult-enriched (37.03 vs 4.10 RPM) but constitutively expressed; a generic cardiomyocyte-immaturity signature therefore does not explain the whole arm, and an immaturity contribution cannot be excluded for *PRSS3*. *GAL* is additionally high in undifferentiated iPSC (102.5 RPM) but not in iPSC-derived cardiomyocytes, so residual undifferentiated cells remain a possible contributor to *GAL* induction. *AL049629.2*, *SPECC1L-ADORA2A* and *MTRNR2L13* are absent from this matrix (lncRNA / fusion / mitochondrial transcript annotation).

Gene	Program direction	hiPSC-CM (n=3)	iPSC (n=3)	Fetal heart (n=1)	Adult heart (n=3)
GAL	up	0.54	102.53	0.85	0.05
PAEP	up	0.00	0.00	0.16	0.00
AL049629.2	up	not in matrix	—	—	—
PMCH	up	0.00	0.00	0.00	0.00
MUSTN1	up	0.51	2.96	4.10	37.03

Gene	Program direction	hiPSC-CM (n=3)	iPSC (n=3)	Fetal heart (n=1)	Adult heart (n=3)
PRSS3	up	0.05	1.06	6.97	0.15
MTRNR2L13	up	not in matrix	—	—	—
VAT1L	down	18.68	35.04	28.09	11.52
COL10A1	down	0.05	0.05	0.54	0.32
CNTN1	down	22.29	6.62	41.25	0.51
SPECC1L-ADORA2A	down	not in matrix	—	—	—
TMEM130	down	0.00	2.27	0.70	0.22
SMOC2	down	0.00	15.42	312.03	75.79
COMP	down	0.00	0.17	1.39	8.23
RGS7BP	down	3.63	3.72	97.28	8.64

Supplementary Table S13. Leave-one-donor-out sensitivity of the 15 candidate genes (donor-level, Myo+SD+ vs HC; primary DESeq2 settings)

The donor-level DESeq2 comparison was repeated with each of the 14 donors held out in turn, using the same settings as the primary donor-level analysis (summed raw counts per donor, DESeq2 default independent filtering). The 'full' columns therefore reproduce Figure 3C and Table 1 exactly (e.g. *GAL* padj = 0.0273, *VAT1L* = 6.8×10^{-4}); *PAEP*, *PMCH*, *MTRNR2L13*, *MUSTN1* and *RGS7BP* have no adjusted p-value in the primary run because they were removed by independent filtering, and are shown as n.a. Direction of change was stable for all 15 genes across all folds. A separate sensitivity analysis that retained independently filtered genes is reported in Supplementary Table S11; in that alternative preprocessing *PAEP*, *PMCH* and *MTRNR2L13* receive adjusted p-values, which is why that table counts 7 versus 10 significant genes. Neither run changes the direction of any gene.

Gene	Donor log2FC (full)	Donor padj (full)	log2FC range (LODO)	padj range (LODO)	Direction stable	Folds with FDR < 0.05 (of 14)
GAL	2.528	0.0273	2.084 to 3.101	0.01 to 0.125	Yes	9
PAEP	2.055	n.a.	1.426 to 2.356	0.00152 to 0.0413	Yes	7
AL049629.2	1.524	0.00868	1.142 to 2.008	0.00362 to 0.1	Yes	10
PMCH	1.658	n.a.	1.283 to 2.02	0.0224 to 0.12	Yes	5
MUSTN1	1.673	n.a.	0.111 to 2.445	0.116 to 0.221	Yes	0
PRSS3	1.548	0.00955	1.264 to 2.025	0.00264 to 0.0724	Yes	12

Gene	Donor log2FC (full)	Donor padj (full)	log2FC range (LODO)	padj range (LODO)	Direction stable	Folds with FDR < 0.05 (of 14)
MTRNR2L13	1.171	n.a.	0.984 to 1.338	0.00803 to 0.0302	Yes	4
VAT1L	-1.329	6.8e-4	-1.563 to -0.894	7.8e-5 to 0.0307	Yes	14
COL10A1	-2.457	0.0154	-3.305 to -2.093	5.9e-5 to 0.106	Yes	10
CNTN1	-1.266	0.0112	-1.607 to -0.964	0.00233 to 0.0545	Yes	10
SPECC1L-ADORA2A	-1.837	3.5e-7	-2.031 to -1.586	2.4e-8 to 3.2e-4	Yes	13
TMEM130	-1.244	0.15	-1.796 to -0.714	0.0454 to 0.499	Yes	1
SMOC2	-1.183	0.165	-1.646 to -0.436	0.0786 to 0.673	Yes	0
COMP	-1.122	0.167	-1.494 to -0.631	0.109 to 0.541	Yes	0
RGS7BP	-1.081	n.a.	-1.404 to -0.796	0.0486 to 0.118	Yes	1

Supplementary Table S14. Permutation analyses: locked-score test versus fully nested pipeline permutation (donor level)

The fully nested p of 0.194 is conditional on the 1,289 permutations in which at least one Tier-1 gene was identified; counting the 711 permutations without a Tier-1 gene as non-extreme gives an unconditional p of 0.125. A stricter variant of the nested analysis, restricted to the 304 permutations in which all 14 folds returned a feature set, removes any dependence on the handling of empty folds: its null mean is 0.449 and the observed 7/14 gives P = 0.397.

The locked-score permutation enumerates all C(14,4) = 1,001 donor-level label assignments for the fixed 12-gene score, with the three replicates of each donor treated as a single label block. In the fully nested analyses each of the following steps was repeated within every permutation: differential-expression screening, Tier-1 intersection, direction assignment, score construction and cut-off selection. The composition of the 12-gene core itself was not re-selected inside the folds (it was chosen after inspecting donor-level significance in the full dataset). The nested estimate therefore uses, in every fold, the fold-specific Tier-1 panel, which contained between 2 and 69 genes, and does not use the 12-gene core. 2,000 permutations were used for the donor-level AUC of the pipeline-derived score and 1,000 for the nested leave-one-donor-out cross-validation (LODO-CV) accuracy (974 evaluable), with group sizes (3/3/4/4) preserved across donors. Permutations in which no Tier-1 gene was identified were non-evaluable and were excluded from the denominator; empirical p = (1 + k)/(1 + N_evaluable). For the pipeline AUC, 249 of the 1,289 evaluable permutations reached AUC = 1.000, i.e. the null distribution is concentrated at the ceiling; for nested

LODO-CV the observed accuracy (0.500) was not distinguishable from its permutation null (mean 0.364, maximum 1.000, p = 0.286, or p = 0.591 when empty folds were scored as majority-class calls). Of the 1,000 permutations, 26 contained no evaluable fold and are counted as non-extreme in p = 0.279, whereas restricting the null to the 304 permutations in which every fold was evaluable gives p = 0.397. The locked-score p value therefore refers to the fixed gene set only and does not extend to the discovery pipeline as a whole.

Analysis	Test statistic	Permutations (evaluable)	Observed	Null mean	Null max	Empirical p
Locked-score permutation (exact enumeration)	Donor-level AUC, fixed 12-gene score	1,001 (all)	1.000	0.500	1.000	0.0010
Fully nested, pipeline AUC (Part A)	Donor-level AUC, pipeline re-run in every permutation	1,289 of 2,000	1.000	0.871	1.000	0.194
Fully nested, nested LODO-CV (Part B), primary rule	Nested LODO-CV accuracy, selection repeated each fold and permutation	1,000 (974 evaluable)	0.500	0.364	1.000	0.286
Fully nested, nested LODO-CV (Part B), empty folds imputed	Nested LODO-CV accuracy, empty selection scored as majority class	1,000 (1000 evaluable)	0.500	0.511	0.929	0.591

Supplementary Table S15. Etiology-resolved program score in GSE116250 (signed ssGSEA, 15-gene candidate program)

Signed ssGSEA scores (up-regulated minus down-regulated genes) were computed with the same scoring function used for the archived external analysis; six of the seven up-regulated genes and all eight down-regulated genes were represented in this RNA-seq dataset. Effects are Hedges' g with small-sample correction, computed against non-failing (NF) hearts. The pooled comparison (all HF versus NF, g = -0.472) reproduces the GSE116250 effect used in the manuscript meta-analysis, confirming that the scoring pipeline is identical; the two etiologies are reported separately here so that the absent reactivity cannot be attributed to pooling. No etiology shows elevation of the program score, which supports contextual distinction from conventional heart-failure programs while not establishing SLE-HF myocardial specificity.

Comparison	Hedges' g	SE	n (cases)	n (controls)

Dilated cardiomyopathy vs non-failing	-0.587	0.314	37	14
Ischemic cardiomyopathy vs non-failing	-0.273	0.375	13	14
All heart failure vs non-failing (replication check)	-0.472	0.302	50	14

Note: with 18,106 expressed genes and a 15-gene program, the expected number of shared genes is 15 × |set| / 18,106 = 0.016–0.026 for the set sizes used here, and the probability of observing no overlap at all is 0.975–0.984 under the hypergeometric null. A Jaccard index of 0 is therefore the default outcome rather than positive evidence, and is reported for completeness only; the non-canonical character of the candidate program rests on the pathway and regulon analyses.

Supplementary Table S16. Donor-level correlations of the candidate program score with GDMT-related and immune-pathway scores, with member-gene coverage

Pathway scores were recomputed by ssGSEA on donor pseudobulk profiles (normalized counts summed across the three EHM replicates of each donor) and correlated with the locked donor-level program score by Spearman correlation across 14 donors; p values are Benjamini-Hochberg corrected within each family (eight GDMT pathways, eight immune pathways). 'Mean-replicate' gives the same correlation using the average of the three per-sample scores per donor as a sensitivity analysis. Coverage is the number of member genes detected in the EHM expression matrix (and, in parentheses, the number passing the expression filter), against the curated set size. The corresponding sample-level (n = 42) estimates are given in Supplementary Tables S7 and S9.

GDMT-related pathways

Pathway	Genes detected / total	Spearman ϱ (donor)	p	FDR	Mean-replicate ϱ	Mean-replicate p
β-adrenergic	22 / 24	-0.842	0.000225	0.0018	-0.851	0.000136
SGLT2i Metabolic	25 / 25	-0.789	0.00128	0.00513	-0.758	0.00252
Natriuretic cGMP	10 / 10	-0.745	0.00325	0.00867	-0.723	0.00481
GPCR internalization	14 / 16	0.411	0.146	0.233	0.411	0.146
MR SGK1	10 / 12	-0.481	0.084	0.168	-0.473	0.0904
IFN JAK STAT	22 / 22	-0.332	0.246	0.321	-0.288	0.318
Ca handling	10 / 10	-0.31	0.281	0.321	-0.332	0.246
RAAS	15 / 19	0.222	0.445	0.445	0.178	0.542

Immune pathways

Pathway	Genes detected / total	Spearman ϱ (donor)	p	FDR	Mean-replicate ϱ	Mean-replicate p
TGFβ signaling	14 / 16	-0.688	0.00838	0.0671	-0.684	0.00894
Chemokine	13 / 22	0.547	0.0459	0.183	0.547	0.0459
Antigen presentation	17 / 19	0.451	0.108	0.288	0.429	0.128
Complement	17 / 20	-0.182	0.532	0.62	-0.143	0.627
TNF NFKB	13 / 14	0.319	0.267	0.533	0.319	0.267
Interferon response	20 / 20	-0.116	0.693	0.693	-0.099	0.739
IL1 inflammasome	12 / 13	0.191	0.512	0.62	0.196	0.502
Fc receptor	2 / 7	0.178	0.542	0.62	0.187	0.522

Supplementary Table S17. Adult-heart baseline expression of the 15 candidate genes (GTEx v8, median TPM)

Median expression in GTEx v8 heart left ventricle and atrial appendage. Genes with <0.1 TPM in left ventricle are considered essentially silent, which is the criterion used for the biological prioritization of *GAL*. Note that the program is not uniformly 'adult-silent': *MUSTN1*, *SMOC2* and *VAT1L* are constitutively expressed in adult heart. *AL049629.2* is absent from the GTEx v8 gene model and *SPECC1L-ADORA2A* is not quantified in GTEx v8, so these two cannot be evaluated in this resource.

Gene	Left ventricle (TPM)	Atrial appendage (TPM)	Comment
GAL	0.063	0.082	
PAEP	0.000	0.000	
AL049629.2	n.a.	n.a.	not present in the GTEx v8 gene model
PMCH	0.000	0.000	
MUSTN1	22.975	65.328	constitutively expressed in adult heart
PRSS3	0.062	0.106	
MTRNR2L13	0.000	0.000	
VAT1L	2.350	5.246	constitutively expressed in adult heart
COL10A1	0.043	0.052	
CNTN1	0.053	0.219	
SPECC1L-ADORA2A	n.a.	n.a.	read-through locus; not quantified in GTEx v8
RGS7BP	0.318	1.141	
TMEM130	0.046	0.168	

Gene	Left ventricle (TPM)	Atrial appendage (TPM)	Comment
SMOC2	12.594	21.970	constitutively expressed in adult heart
COMP	0.662	16.825	

Supplementary Table S18. Scoring-variant sensitivity analysis

Note on metrics: 'cross-validated accuracy' here is the 42-sample accuracy obtained with donor-held-out thresholds, not the donor-level leave-one-donor-out accuracy of Results 2.3 (9 of 14). The bootstrap AUC column is descriptive (Table S10 contains the corresponding distribution). The bootstrap confidence interval of the pooled AUC is not reported because it is degenerate at 1.000.

Internal metrics for the locked program score computed with four gene sets: all 15 candidate genes, the 12-gene scoring core used in the main analysis, the seven donor-level-significant genes, and the ten genes that were significant in the donor-level rerun. The discriminant metric is the bootstrap AUC of the locked score; 'cross-validated accuracy' is the sample-level accuracy (42 samples) obtained with donor-held-out thresholds, not the donor-level leave-one-donor-out accuracy reported in Results 2.3. All four variants give equivalent internal metrics, so no conclusion depends on the choice of core.

Gene set	Genes	Sample-level bootstrap AUC (42 samples)	Cross-validated accuracy
15-gene program	15	0.978	0.619
12-gene scoring core	12	0.981	0.643
7 genes, primary analysis	7	0.983	0.643
10 genes, alternative preprocessing	10	0.978	0.643

Supplementary Table S19. Donor-level coordination of the 15-gene candidate program

(A) Direction-aware pairwise Spearman correlations within the seven up-regulated genes, within the eight down-regulated genes, and between the two arms, computed on donor pseudobulk profiles (n = 14 donors) and, for comparison, on the 42 EHM samples and on GSE116250 left-ventricular tissue. P values come from 10,000 random gene sets of the same size drawn from genes matched on mean-expression decile. (B) Per-gene consistency: Spearman correlation between each gene's donor-level profile and the locked donor-level program score; the expected sign is positive for up-regulated and negative for down-regulated genes. n.a. = fewer than two genes with non-zero variance in that subset.

(A) Coordination metrics

Analysis	within up arm (ϱ)	within down arm (ϱ)	between arms (ϱ)	p (up)	p (down)	p (between)	genes (up/down)
EHM donor level (n=14)	0.462	0.656	-0.439	0.0004	0.0001	0.0001	7/8
EHM sample level (n=42)	0.386	0.504	-0.318	0.002	0.0005	0.0005	7/8
GSE116250 non-failing	-0.002	0.062	0.053	n.a.	n.a.	n.a.	6/8
GSE116250 DCM	n.a.	0.192	n.a.	n.a.	n.a.	n.a.	6/8
GSE116250 ICM	n.a.	0.134	n.a.	n.a.	n.a.	n.a.	6/8

(B) Per-gene consistency at the donor level

Gene	Arm	ϱ with donor-level program score	Expected direction
GAL	up	0.719	yes
PAEP	up	0.912	yes
AL049629.2	up	0.767	yes
PMCH	up	0.582	yes
MUSTN1	up	0.042	yes
PRSS3	up	0.64	yes
MTRNR2L13	up	0.547	yes
VAT1L	down	-0.916	yes
COL10A1	down	-0.855	yes
CNTN1	down	-0.785	yes
SPECC1L-ADORA2A	down	-0.736	yes
TMEM130	down	-0.789	yes
SMOC2	down	-0.776	yes
COMP	down	-0.653	yes
RGS7BP	down	-0.807	yes

Supplementary Table S20. Per-gene decomposition of the non-SLE HF meta-analytic estimate

Random-effects (REML) meta-analysis of the two evaluable non-SLE HF myocardial cohorts (GSE116250 and GSE57345) for the full 15-gene program, for each of the 15 leave-one-gene-out variants, and for a coding-only formulation that omits *AL049629.2* (lncRNA clone), *MTRNR2L13* (mitochondrially derived) and *SPECC1L-ADORA2A* (read-through

transcript). Direction is negative in every variant; the magnitude and significance are governed by *MTRNR2L13*, whose removal collapses I^2 from 93.4% to 0.0% and shifts g from −1.14 to −1.76. Removing *AL049629.2* alone leaves the estimate unchanged. The full-set row reproduces the value reported in Results 2.6 and Figure 4C.

Gene set	**Genes**	**Hedges' g**	**95% CI**	**p**	**I^2**
full 15-gene program	7+8	-1.144	[-2.406, 0.117]	0.0754	93.4%
leave-one-out: *AL049629.2*	-6+8	-1.144	[-2.406, 0.117]	0.0754	93.4%
leave-one-out: -*CNTN1*	7+7	-1.212	[-2.36, -0.063]	0.0387	92%
leave-one-out: *COL10A1*	-7+7	-1.18	[-2.418, 0.058]	0.0618	93.2%
leave-one-out: -*COMP*	7+7	-1.016	[-2.572, 0.54]	0.201	95.7%
leave-one-out: -*GAL*	6+8	-1.015	[-2.423, 0.393]	0.158	94.8%
leave-one-out: *MTRNR2L13*	-6+8	-1.756	[-1.999, -1.513]	1.96e-45	0%
leave-one-out: *MUSTN1*	-6+8	-0.956	[-2.15, 0.239]	0.117	92.8%
leave-one-out: -*PAEP*	6+8	-1.047	[-2.402, 0.308]	0.13	94.4%
leave-one-out: -*PMCH*	6+8	-1.065	[-2.465, 0.336]	0.136	94.7%
leave-one-out: -*PRSS3*	6+8	-1.105	[-2.445, 0.234]	0.106	94.2%
leave-one-out: -*RGS7BP*	7+7	-1.185	[-2.367, -0.002]	0.0495	92.5%
leave-one-out: -*SMOC2*	7+7	-0.848	[-1.659, -0.036]	0.0406	84.8%
leave-one-out: *SPECC1L-ADORA2A*	-7+7	-1.208	[-2.351, -0.066]	0.0382	91.9%
leave-one-out: *TMEM130*	-7+7	-1.152	[-2.432, 0.127]	0.0776	93.6%

leave-one-out: -*VAT1L*	7+7	-1.153	[-2.536, 0.229]	0.102	94.5%
coding-only (drops *AL049629*.2, *MTRNR2L13*, *SPECC1L-ADORA2*A)	5+7	-1.769	[-2.013, -1.526]	5.88e-46	0%
reduced 12-gene AL049629.2 (13)	+5+8	-1.769	[-2.013, -1.525]	6.32e-46	0.0%
reduced 12-gene SPECC1L-ADORA2A (13)	+5+8	-1.756	[-1.999, -1.513]	2.09e-45	0.0%
reduced 12-gene MTRNR2L13 (13)	+5+8	-1.208	[-2.35, -0.066]	0.0381	91.9%

Supplementary Table S21. Robustness of the 15-gene program to threshold choice, gene removal and substitution of the prioritized candidate

Panel B2 reports the sign (weight-inversion) perturbation. Panel A re-thresholds and panels B/B2 perturb the 15-gene directionally weighted score; the main analysis uses the 12-gene scoring core (Methods 4.7), so these panels document the robustness of the candidate program rather than of the locked 12-gene score.

(A) Genes retained and score correlation when the program is rebuilt at adjacent FDR and |log2FC| thresholds (the operating point used in the manuscript is FDR < 0.05 and |log2FC| > 1). (B) Score correlation after removing each single gene, and after removing one to three genes at random (200 draws). (C) External meta-analytic effect (two cohorts, REML) when *GAL* is removed, when *VAT1L* is removed, and when both are removed. Donor-level LODO accuracy for the swap variants is not tabulated because the reimplementation used for these runs operates at a different decision threshold from the locked-score procedure of Results 2.3; the corresponding internal comparison is therefore qualitative only and the external effects carry the weight of this table.

(A) Re-thresholding within the fixed 15-gene set

Footnote: in panel A the |log2FC| > 1.5, FDR < 0.01 row cannot be scored because only one down-regulated gene survives that threshold; it is reported as n.a. rather than as a correlation.

FDR	|log2FC|	Genes retained	Spearman ϱ vs original score

0.01	0.75	10	0.96
0.05	0.75	15	1
0.1	0.75	15	1
0.01	1	10	0.96
0.05	1	15	1
0.1	1	15	1
0.01	1.5	7	NA
0.05	1.5	8	0.928
0.1	1.5	8	0.928

(B) Composition perturbation (single-gene removal; weight inversion in panel B2)

Removal	Spearman ϱ vs original score
GAL	0.995
PAEP	0.998
AL049629.2	0.994
PMCH	0.994
MUSTN1	0.994
PRSS3	0.995
MTRNR2L13	0.996
VAT1L	0.996
COL10A1	0.997
CNTN1	0.994
SPECC1L-ADORA2A	0.989
TMEM130	0.995
SMOC2	0.995
COMP	0.996
RGS7BP	0.994
random 1-3 genes (median of 200 draws)	0.991
random 1-3 genes (minimum of 200 draws)	0.963

(C) Substitution of the prioritized candidate (external meta-analysis, k = 2)

Variant	Genes	External meta-analytic g
original 15-gene program	15	-1.144
GAL removed	14	-1.015
VAT1L removed	14	-1.153
GAL removed, *VAT1L* as anchor	13	-1.008

(B2) Sign perturbation (inversion of direction weights)

Perturbation	Spearman ρ vs original score
invert weight: *GAL*	0.983
invert weight: *PAEP*	0.99
invert weight: *AL049629*.2	0.983
invert weight: *PMCH*	0.974
invert weight: *MUSTN1*	0.981
invert weight: *PRSS3*	0.974
invert weight: *MTRNR2L13*	0.982
invert weight: *VAT1L*	0.986
invert weight: *COL10A1*	0.987
invert weight: *CNTN1*	0.977
invert weight: *SPECC1L-ADORA2*A	0.974
invert weight: *TMEM130*	0.983
invert weight: *SMOC2*	0.985
invert weight: *COMP*	0.984
invert weight: *RGS7BP*	0.979
random inversion of 1 gene (median of 200)	0.983
random inversion of 2 genes (median of 200)	0.96
random inversion of 3 genes (median of 200)	0.925
random inversion of 1-3 genes (minimum of 200)	0.836

Supplementary Table S22. Alignment of the external datasets with the discovery design, and the reason

Each comparison is contextually informative rather than a validation. The table covers the 13 public datasets used in the study, including GSE81622, which is not part of the prespecified four-cohort meta-analysis and is reported as a five-cohort sensitivity analysis in Supplementary Table S30.

For each external dataset the table records the tissue compartment, the platform, how group labels were defined, whether donor-level structure is available, how the score direction was handled, and which of the three classes of explanation (biological, technical, statistical) applies. No dataset provides SLE-HF myocardium, so none can serve as direct validation.

Dataset	Compartment	Platform	Group definition	Donor-level structure	Gene annotation	Re-standardized?	Direction handling	Explanation

				probe mapping		
GSE116250	Left ventricle (non-failing vs DCM/ICM)	RNA-seq, gene level	Published etiology labels	No (one sample per subject)	Gene symbols as published	No (signed within-cohort ranks)	Signed GSEA, Signed score, direction pre-served	Technical + biological + technical
GSE57345	Left ventricle (non-failing vs DCM/ICM)	Microarray (Affymetrix)	Published etiology labels	No	Probe IDs collapsed to gene symbols (max-mean)	No	Signed score, direction pre-served	Technical (probe coverage)
GSE57338	Left ventricle (non-failing vs DCM/ICM)	Microarray (Affymetrix)	Published etiology labels	No	Probe IDs collapsed to gene symbols	No	Signed score, direction pre-served	Technical (probe coverage) + statistical (small k)
GSE42955	Left ventricle (comparator cohort)	Microarray (Affymetrix)	Published etiology labels	No	Probe IDs collapsed to gene symbols	No	Signed score, direction pre-served	Statistical (comparator, not independent)
GSE141910	Left ventricle	RNA-seq	Published etiology labels	No	Gene symbols as published	No	Not evaluable	Technical (insufficient core-gene detection)
SLE blood cohorts (4: GSE50772, GSE61635,	Whole blood (PBMC	Microarray and RNA-seq	SLE vs control	No	Gene symbols / probe collapse per platform	No	Signed score, direction pre-served	Biological (compartment) + technical

GSE65391, GSE72326)						
GSE303117	Non-SLE HF peripheral blood	RNA-seq	HF vs control	No	Gene sym-bols as pub-lished	Single-gene level only	Biological (compart-ment)
GSE264125	SLE whole blood	RNA-seq	SLE vs con-trol	No	Gene sym-bols as pub-lished	Single gene (*GAL*), di-rection pre-served	Statistical (single-gene level only)
GSE154580	iPSC-CM / fe-tal / adult heart	RNA-seq (RPM)	Develop-mental stage	No	Gene sym-bols as pub-lished	Absolute expression, no score	Technical (model ma-turity; sin-gle fetal sample)
GSE81622	Whole blood	Microarray	SLE vs con-trol	No	Probe col-lapse to gene symbols	Not evalu-ated	Statistical (not in pre-specified set; sensi-tivity in Ta-ble S30)

Supplementary Table S23. Member-gene associations with the candidate program score for the eight curated immune pathways.

Spearman correlations between each detected member gene and the locked 12-gene program score, computed at the sample level (n = 42 samples; log2 normalized counts) and at the donor level (n = 14 donors; donor pseudobulk formed by summing the three replicate profiles, log2). Benjamini–Hochberg FDR was computed within each pathway's detected member genes. Direction compares the sign of the gene-level correlation with the sign of the corresponding pathway-level correlation (sample level: Supplementary Table S9; donor level: Supplementary Table S16). Panel A lists every detected member gene; panel B summarizes same- and opposite-direction genes per pathway. These correlations

describe co-variation inside one in vitro dataset and do not establish pathway activity in SLE-HF myocardium.

(A) Per-gene results

Pathway	Gene	ϱ (sample)	FDR (sample)	Direction (sample)	ϱ (donor)	FDR (donor)	Direction (donor)
TGFβ signaling	*SMAD3*	0.207	0.239	opposite	0.209	0.603	opposite
TGFβ signaling	*SERPINE1*	0.182	0.291	opposite	0.112	0.757	opposite
TGFβ signaling	*TAGLN*	0.040	0.803	opposite	-0.002	0.994	same
TGFβ signaling	*COL1A1*	-0.083	0.648	same	-0.169	0.657	same
TGFβ signaling	*TGFB3*	-0.242	0.172	same	-0.275	0.479	same
TGFβ signaling	*ACTA2*	-0.310	0.0708	same	-0.301	0.46	same
TGFβ signaling	*CDH2*	-0.383	0.0215	same	-0.538	0.11	same
TGFβ signaling	*TGFB2*	-0.435	0.008	same	-0.508	0.128	same
TGFβ signaling	*FN1*	-0.481	0.00296	same	-0.486	0.137	same
TGFβ signaling	*SMAD2*	-0.484	0.00296	same	-0.591	0.0767	same
TGFβ signaling	*TGFBR2*	-0.504	0.00236	same	-0.587	0.0767	same
TGFβ signaling	*SMAD7*	-0.524	0.00175	same	-0.640	0.0767	same
TGFβ signaling	*TGFBR1*	-0.548	0.00121	same	-0.618	0.0767	same
TGFβ signaling	*SMAD4*	-0.606	0.000291	same	-0.754	0.0258	same
Chemokine signaling	*CXCL1*	0.532	0.00203	same	0.705	0.0627	same
Chemokine signaling	*CXCL8*	0.529	0.00203	same	0.587	0.119	same
Chemokine signaling	*CCL2*	0.499	0.00337	same	0.609	0.119	same
Chemokine signaling	*CXCL2*	0.313	0.114	same	0.495	0.235	same
Chemokine signaling	*CCR7*	0.237	0.234	same	0.270	0.569	same
Chemokine signaling	*CCL7*	0.107	0.56	same	0.169	0.813	same
Chemokine signaling	*CCL20*	-0.061	0.703	opposite	-0.042	0.887	opposite
Chemokine signaling	*CCL8*	-0.103	0.56	opposite	-0.051	0.887	opposite
Chemokine signaling	*CXCL10*	-0.186	0.309	opposite	-0.108	0.844	opposite
Chemokine signaling	*CXCR4*	-0.189	0.309	opposite	-0.429	0.259	opposite

Pathway	Gene	ϱ (sample)	FDR (sample)	Direction (sample)	ϱ (donor)	FDR (donor)	Direction (donor)
Chemokine signaling	*CXCL16*	-0.229	0.234	opposite	-0.121	0.844	opposite
Chemokine signaling	*CCL5*	-0.288	0.14	opposite	-0.451	0.259	opposite
Chemokine signaling	*CX3CR1*	-0.476	0.00472	opposite	-0.415	0.259	opposite
Complement	*CD59*	0.693	6e-06	opposite	0.771	0.021	opposite
Complement	*C4B*	0.431	0.0185	opposite	0.451	0.45	opposite
Complement	*MASP1*	0.177	0.372	opposite	0.297	0.726	opposite
Complement	*CD55*	0.147	0.427	opposite	0.077	0.843	opposite
Complement	*C4A*	0.111	0.55	opposite	0.130	0.797	opposite
Complement	*CFI*	0.025	0.876	opposite	0.160	0.763	opposite
Complement	*C2*	-0.099	0.564	same	-0.235	0.762	same
Complement	*MASP2*	-0.165	0.389	same	0.112	0.797	opposite
Complement	*CFD*	-0.194	0.336	same	-0.046	0.876	same
Complement	*C1R*	-0.216	0.288	same	-0.169	0.763	same
Complement	*CFB*	-0.286	0.125	same	-0.275	0.726	same
Complement	*C3*	-0.294	0.125	same	-0.341	0.661	same
Complement	*CD46*	-0.297	0.125	same	-0.200	0.762	same
Complement	*C5*	-0.338	0.0803	same	-0.200	0.762	same
Complement	*CFH*	-0.407	0.0256	same	-0.389	0.575	same
Complement	*C1S*	-0.468	0.0101	same	-0.486	0.444	same
Complement	*SERPING1*	-0.487	0.00906	same	-0.552	0.347	same
Antigen presentation	*HLA-DPB1*	0.486	0.00938	same	0.560	0.209	same
Antigen presentation	*HLA-DPA1*	0.474	0.00938	same	0.543	0.209	same
Antigen presentation	*HLA-C*	0.454	0.0108	same	0.371	0.325	same
Antigen presentation	*PSMB8*	0.421	0.0156	same	0.486	0.214	same
Antigen presentation	*B2M*	0.411	0.0167	same	0.420	0.255	same
Antigen presentation	*HLA-A*	0.340	0.059	same	0.279	0.405	same
Antigen presentation	*TAP1*	0.328	0.0646	same	0.279	0.405	same

Pathway	Gene	ϱ (sample)	FDR (sample)	Direction (sample)	ϱ (donor)	FDR (donor)	Direction (donor)
Antigen presentation	*HLA-B*	0.317	0.0697	same	0.266	0.406	same
Antigen presentation	*TAP2*	0.276	0.101	same	0.314	0.405	same
Antigen presentation	*PSMB9*	0.137	0.41	same	0.143	0.626	same
Antigen presentation	*HLA-DQB1*	0.059	0.709	same	0.288	0.405	same
Antigen presentation	*CIITA*	-0.157	0.364	opposite	-0.600	0.209	opposite
Antigen presentation	*HLA-DRB1*	-0.186	0.288	opposite	-0.209	0.503	opposite
Antigen presentation	*CD74*	-0.288	0.0918	opposite	-0.473	0.214	opposite
Antigen presentation	*HLA-DQA1*	-0.297	0.0868	opposite	-0.534	0.209	opposite
Antigen presentation	*HLA-DMA*	-0.427	0.0156	opposite	-0.499	0.214	opposite
Antigen presentation	*TAPBP*	-0.471	0.00938	opposite	-0.424	0.255	opposite
Fc receptor	*FCGR1A*	0.185	0.242	same	0.204	0.771	same
Fc receptor	*FCGR2A*	-0.192	0.242	opposite	-0.086	0.771	opposite
IL-1 / inflammasome	*IRAK1*	0.628	0.000103	same	0.727	0.0383	same
IL-1 / inflammasome	*IL1B*	0.576	0.000393	same	0.675	0.0487	same
IL-1 / inflammasome	*IL18*	0.161	0.488	same	0.358	0.457	same
IL-1 / inflammasome	*PYCARD*	0.155	0.488	same	0.319	0.457	same
IL-1 / inflammasome	*CASP1*	-0.018	0.912	opposite	0.152	0.806	same
IL-1 / inflammasome	*IL1A*	-0.054	0.803	opposite	-0.095	0.816	opposite
IL-1 / inflammasome	*MYD88*	-0.077	0.754	opposite	0.051	0.864	same
IL-1 / inflammasome	*IL1RAP*	-0.118	0.61	opposite	-0.231	0.641	opposite
IL-1 / inflammasome	*NLRP3*	-0.158	0.488	opposite	0.108	0.816	same
IL-1 / inflammasome	*NLRC4*	-0.167	0.488	opposite	-0.393	0.457	opposite
IL-1 / inflammasome	*IL1R1*	-0.281	0.215	opposite	-0.319	0.457	opposite
IL-1 / inflammasome	*IRAK4*	-0.371	0.0626	opposite	-0.363	0.457	opposite
TNF / NF-κB	*IKBKB*	0.596	0.000398	same	0.613	0.064	same
TNF / NF-κB	*IKBKG*	0.515	0.00269	same	0.429	0.164	same
TNF / NF-κB	*NFKB2*	0.492	0.00269	same	0.543	0.0972	same

Pathway	Gene	ϱ (sample)	FDR (sample)	Direction (sample)	ϱ (donor)	FDR (donor)	Direction (donor)
TNF / NF-κB	*TNFRSF1A*	0.490	0.00269	same	0.635	0.064	same
TNF / NF-κB	*RELA*	0.488	0.00269	same	0.407	0.176	same
TNF / NF-κB	*RELB*	0.456	0.00447	same	0.591	0.0675	same
TNF / NF-κB	*TRAF2*	0.369	0.021	same	0.495	0.134	same
TNF / NF-κB	*TNFAIP3*	-0.118	0.456	opposite	-0.165	0.573	opposite
TNF / NF-κB	*TNFRSF1B*	-0.172	0.299	opposite	-0.327	0.274	opposite
TNF / NF-κB	*TRAF6*	-0.344	0.0304	opposite	-0.648	0.064	opposite
TNF / NF-κB	*RIPK1*	-0.420	0.00809	opposite	-0.459	0.16	opposite
TNF / NF-κB	*CHUK*	-0.443	0.00541	opposite	-0.437	0.164	opposite
TNF / NF-κB	*NFKB1*	-0.472	0.00351	opposite	-0.626	0.064	opposite
Interferon	*IRF3*	0.641	9.7e-05	opposite	0.679	0.0919	opposite
Interferon	*IRF1*	0.590	0.000392	opposite	0.587	0.137	opposite
Interferon	*IRF9*	0.403	0.0325	opposite	0.385	0.317	opposite
Interferon	*IRF7*	0.282	0.156	opposite	0.191	0.615	opposite
Interferon	*ISG15*	0.270	0.169	opposite	0.130	0.732	opposite
Interferon	*IFI44*	0.084	0.705	opposite	-0.015	0.958	same
Interferon	*OASL*	-0.052	0.745	same	0.015	0.958	opposite
Interferon	*IFIT2*	-0.053	0.745	same	-0.187	0.615	same
Interferon	*IFIT3*	-0.073	0.717	same	-0.279	0.477	same
Interferon	*IFIT1*	-0.104	0.641	same	-0.323	0.432	same
Interferon	*OAS1*	-0.133	0.535	same	-0.464	0.316	same
Interferon	*MX1*	-0.155	0.466	same	-0.310	0.432	same
Interferon	*OAS3*	-0.196	0.33	same	-0.196	0.615	same
Interferon	*IFI44L*	-0.219	0.272	same	-0.398	0.317	same
Interferon	*DDX58*	-0.251	0.198	same	-0.477	0.316	same
Interferon	*OAS2*	-0.326	0.0878	same	-0.420	0.317	same
Interferon	*MX2*	-0.327	0.0878	same	-0.389	0.317	same

Pathway	Gene	ϱ (sample)	FDR (sample)	Direction (sample)	ϱ (donor)	FDR (donor)	Direction (donor)
Interferon	*IFIH1*	-0.377	0.0463	same	-0.640	0.0919	same
Interferon	*STAT2*	-0.409	0.0325	same	-0.429	0.317	same
Interferon	*STAT1*	-0.472	0.0106	same	-0.644	0.0919	same

(B) Per-pathway summary (opposite direction = sign of the gene-level correlation differs from the sign of the pathway-level correlation)

Pathway	Members tected	de- Same direction, FDR < 0.05 (sample)	Opposite direc-tion, FDR < 0.05 (sample)	Lowest oppo-site-direction FDR (sample)	Same direction, FDR < 0.05 (donor)	Opposite direc-tion, FDR < 0.05 (donor)
TGFβ signaling	14	8	0	0.239	1	0
Chemokine sig-naling	13	3	1	0.00472	0	0
Complement	17	3	2	6e-06	0	1
Antigen presen-tation	17	5	2	0.00938	0	0
Fc receptor	2	0	0	0.242	0	0
IL-1 / inflam-masome	12	2	0	0.0626	2	0
TNF / NF-κB	13	7	4	0.00351	0	0

Pathway	Members	de-Same direction, FDR < 0.05 (sam-ple)	Opposite direc-tion, FDR < 0.05 (sample)	Lowest oppo-site-direction FDR (sample)	Same direction, FDR < 0.05 (do-nor)	Opposite direc-tion, FDR < 0.05 (donor)
Interferon	20	3	3	9.7e-05	0	0

Key point: pathway-level nulls (Supplementary Tables S9 and S16) do not imply that no member gene co-varies with the candidate program. In the interferon set, IRF3 (ϱ = +0.64, FDR = 9.7×10^{-5}), IRF1 (+0.59, 3.9×10^{-4}) and IRF9 (+0.40, 0.032) correlate positively with the program score while STAT1 (−0.47) and STAT2 (−0.41) correlate negatively, and opposite-direction genes reaching FDR < 0.05 also occur in the complement (CD59, ϱ = +0.69), NF-κB (NFKB1, −0.47), antigen-presentation (TAPBP, −0.47) and chemokine (CX3CR1, −0.48) sets. At the donor level, CD59 remains opposite-direction significant (ϱ = +0.77, FDR = 0.021).

Supplementary Table S24. Targeted cardiac-adrenergic and fibrosis/ECM gene-set check.

The MSigDB collection used for the primary analysis (CP:KEGG_LEGACY, 186 sets) does not contain the KEGG map "Adrenergic signaling in cardiomyocytes" (hsa04261) and contains no fibrosis or extracellular-matrix set, so the corresponding statements in Results 2.4 are supported here by a dedicated panel: current KEGG maps retrieved from the KEGG REST API on 2026-10-24 (adrenergic signaling, dilated and hypertrophic cardiomyopathy, cardiac muscle contraction, calcium, cAMP and cGMP–PKG signaling) and curated fibrosis/ECM sets from MSigDB (Reactome, Hallmark, GO:BP and WikiPathways). The same ranked list (DESeq2 Wald statistic, Myo+SD+ vs HC, 42 samples) and the same settings as Supplementary Figure S2 were used (fgseaMultilevel, minSize 10, maxSize 500, seed 42); FDR is Benjamini–Hochberg across the 17 sets of this panel. Because these KEGG maps are the current REST versions, their gene sets differ from the MSigDB CP:KEGG_LEGACY sets used in the primary analysis (Supplementary Figure S2); the same pathway name can therefore yield a different NES in the two collections (for example dilated and hypertrophic cardiomyopathy), and only comparisons within one collection are meaningful.

Gene set	Source	Genes in matrix	NES	p	FDR (panel)
Cardiac muscle contraction (hsa04260)	KEGG (live REST, 2026-10-24)	75	+1.52	0.00911	0.077
Response to TGF-β (GO:BP)	MSigDB curated	260	−1.41	0.00181	0.031
Adrenergic signaling in cardiomyocytes (hsa04261)	KEGG (live REST, 2026-10-24)	140	+1.41	0.0155	0.088
Pro-inflammatory and pro-fibrotic mediators (WikiPathways)	MSigDB curated	58	+1.18	0.182	0.773
Dilated cardiomyopathy (hsa05410)	KEGG (live REST, 2026-10-24)	89	−1.03	0.374	0.914
cGMP–PKG signaling pathway (hsa04022)	KEGG (live REST, 2026-10-24)	152	+1.02	0.405	0.914
Collagen biosynthesis and modifying enzymes (Reactome)	MSigDB curated	64	−1.01	0.416	0.914
Extracellular matrix organization (Reactome)	MSigDB curated	294	−0.99	0.502	0.914
TGF-β signaling (Hallmark)	MSigDB curated	53	−0.95	0.546	0.914
cAMP signaling pathway (hsa04024)	KEGG (live REST, 2026-10-24)	189	+0.92	0.656	0.914
Hypertrophic cardiomyopathy (hsa05414)	KEGG (live REST, 2026-10-24)	94	+0.89	0.672	0.914
Epithelial–mesenchymal transition (Hallmark)	MSigDB curated	198	+0.86	0.787	0.914
Collagen formation (Reactome)	MSigDB curated	85	−0.85	0.807	0.914
Degradation of the extracellular matrix (Reactome)	MSigDB curated	125	−0.82	0.855	0.914
Lung fibrosis (WikiPathways)	MSigDB curated	44	+0.82	0.764	0.914
Collagen fibril organization (GO:BP)	MSigDB curated	77	−0.81	0.86	0.914
Calcium signaling pathway (hsa04020)	KEGG (live REST, 2026-10-24)	220	+0.80	0.914	0.914

Reading. NES > 0 indicates enrichment in the Myo+SD+ direction. Adrenergic signaling and cardiac muscle contraction trended positive but did not survive panel-level correction (FDR 0.088 and 0.077); calcium signaling, dilated and hypertrophic cardiomyopathy were not significant. No fibrosis/ECM set showed significant positive enrichment, and the broad GO response-to-TGF-β set was significantly negative (NES −1.41, FDR 0.031), consistent with the inverse TGF-β association reported in Results 2.9. These results do not

support a canonical heart-failure program signature and provide no evidence of fibrotic/ECM activation in the model.

Supplementary Table S25. Summary of donor-level significance, sample-level support and external single-gene evidence for the 15 candidate genes.

Categories: (i) donor-level FDR < 0.05 under the primary DESeq2 settings; (ii) tested at donor level but not significant (sample-level association only); (iii) not testable at donor level because the gene was removed by independent filtering (padj not assigned), so donor-level significance could not be assessed. Donor-level FDR and the number of leave-one-donor-out folds reaching FDR < 0.05 are from Supplementary Table S13; sample-level values are from Table 1/Supplementary Table S3. External single-gene evidence is listed only where a single-gene test exists; for all 15 genes the external program-level estimate is given in Results 2.6 and Supplementary Tables S1 and S20. n.a., not assessable. The fold count refers to the leave-one-donor-out re-analysis (Supplementary Table S13), in which a gene removed in the full-cohort run can still be assessable in some folds.

Gene	Functional group	Sample-level log2FC (FDR)	Donor-level FDR (primary)	LODO folds with donor-level FDR < 0.05	Category	External single-gene evidence
GAL	Ectopic secreted signalling	+2.56 (3.52e-05)	0.0273	9/14	(i) donor-level significant	GSE264125 (SLE blood): +2.00, p = 0.008
AL049629.2	Non-coding / uncharacterised	+1.54 (2.98e-05)	0.00868	10/14	(i) donor-level significant	none
PRSS3	Secreted protease / ECM remodeling	+1.59 (4.03e-04)	0.00955	12/14	(i) donor-level significant	none
VAT1L	Metabolic / uncharacterised	-1.35 (2.01e-06)	6.80e-04	14/14	(i) donor-level significant	none
COL10A1	ECM remodelling	-2.42 (4.00e-05)	0.0154	10/14	(i) donor-level significant	none
CNTN1	GPCR signalling / adhesion	-1.29 (1.18e-04)	0.0112	10/14	(i) donor-level significant	none
SPECC1L-ADORA2A	Non-coding / uncharacterised	-1.84 (0.0127)	3.51e-07	13/14	(i) donor-level significant	none

Gene	Functional group	Sample-level log2FC (FDR)	Donor-level FDR (primary)	LODO folds with donor-level FDR < 0.05	Category	External single-gene evidence
TMEM130	Uncharacterised membrane	-1.23 (0.0135)	0.15	1/14	(ii) sample-level only (tested, not significant at donor level)	none
SMOC2	ECM remodelling	-1.18 (0.027)	0.165	0/14	(ii) sample-level only (tested, not significant at donor level)	none
COMP	ECM remodelling	-1.11 (0.0302)	0.167	0/14	(ii) sample-level only (tested, not significant at donor level)	none
PAEP	Ectopic secreted signalling	+2.09 (3.33e-05)	n.a.	7/14	(iii) not testable at donor level (removed by independent filtering)	none
PMCH	Ectopic secreted signalling	+1.70 (0.00211)	n.a.	5/14	(iii) not testable at donor level (removed by independent filtering)	none
MUSTN1	Stress / damage	+1.66 (0.00181)	n.a.	0/14	(iii) not testable at donor level (removed by independent filtering)	GSE303117 (HF blood): p = 0.042

Gene	Functional group	Sample-level log2FC (FDR)	Donor-level FDR (primary)	LODO folds with donor-level FDR < 0.05	Category	External single-gene evidence
MTRNR2L13	Stress / damage	+1.18 (5.60e-04)	n.a.	4/14	(iii) not testable at donor level (removed by independent filtering)	none
RGS7BP	GPCR signalling / adhesion	-1.08 (0.0234)	n.a.	1/14	(iii) not testable at donor level (removed by independent filtering)	GSE303117 (HF blood): p = 0.041

Supplementary Table S26. Donor-level classification of the full panel and of the donor-significant subsets.

The locked score was recomputed for each gene set; z-score parameters and the cut-off (median of the training non-Myo+SD+ donor scores) were re-estimated in the 13 training donors of each leave-one-donor-out fold. 95% intervals: Clopper–Pearson for sensitivity, specificity and accuracy; stratified donor bootstrap (10,000 resamples of the 14 donors within group strata) for balanced accuracy. The Wilson-score column gives the Wilson score intervals for accuracy, which are the intervals quoted in the main text (9/14: 38.8-83.7; nested 7/14: 26.8-73.2). NIR = no-information rate (10/14 = 0.714). Gene directions were taken from the full-cohort donor-level contrast and held fixed across folds; only the z-score parameters and the cut-off were re-estimated inside each training set.

Gene set	n	TP	FN	FP	TN	Accuracy (95% CI)	Accuracy, Wilson 95% CI	Sensitivity (95% CI)	Specificity (95% CI)	Balanced accuracy (95% CI)	NIR	Donor-level in-sample AUC
15-gene panel	15	4	0	4	6	0.7143 (0.419-0.916)	0.7143 (0.454-0.883)	1 (0.398-1.000)	0.6 (0.262-0.878)	0.8 (0.650-0.950)	0.7143	**1.000**
12-gene scoring core	12	4	0	5	5	0.6429 (0.351-0.872)	0.6429 (0.388-0.837)	1 (0.398-1.000)	0.5 (0.187-0.813)	0.75 (0.600-0.900)	0.7143	**1.000**

Gene set	n	TP	FN	FP	TN	Accuracy (95% CI)	Accuracy, Wilson 95% CI	Sensitivity (95% CI)	Specificity (95% CI)	Balanced accuracy (95% CI)	NIR	Donor-level in-sample AUC
7 donor-level significant	7	4	0	5	5	0.6429 (0.351-0.872)	0.6429 (0.388-0.837)	1 (0.398-1.000)	0.5 (0.187-0.813)	0.75 (0.600-0.900)	0.7143	**1.000**
10 donor-level significant (rerun)	10	4	0	5	5	0.6429 (0.351-0.872)	0.6429 (0.388-0.837)	1 (0.398-1.000)	0.5 (0.187-0.813)	0.75 (0.600-0.900)	0.7143	**1.000**
VAT1L only	1	4	0	5	5	0.6429 (0.351-0.872)	0.6429 (0.388-0.837)	1 (0.398-1.000)	0.5 (0.187-0.813)	0.75 (0.600-0.900)	0.7143	**1.000**

Supplementary Table S27. Dependence of donor-level classification on the cut-off rule.

The locked 12-gene score (top block) and the fully nested pipeline with feature selection repeated inside each fold (bottom block) were evaluated under five pre-specified rules. All cut-offs are estimated inside the 13-donor training set of each leave-one-donor-out fold.

Pipeline	Cut-off rule	TP	FN	FP	TN	Accuracy	Sensitivity	Specificity	Balanced accuracy	Accuracy (95% CI, Clopper–Pearson)	Sensitivity (95% CI, Clopper–Pearson)	Specificity (95% CI, Clopper–Pearson)
locked score	median of training negatives (primary)	4	0	5	5	0.6429	1	0.5	0.75	**(0.351-0.872)**	**(0.398-1.000)**	**(0.187-0.813)**
locked score	75th percentile of training negatives	4	0	3	7	0.7857	1	0.7	0.85	**(0.492-0.953)**	**(0.398-1.000)**	**(0.348-0.933)**
locked score	90th percentile of training negatives	4	0	1	9	0.9286	1	0.9	0.95	**(0.661-0.998)**	**(0.398-1.000)**	**(0.555-0.997)**

Pipeline	Cut-off rule	TP	FN	FP	TN	Accuracy	Sensitivity	Specificity	Balanced accuracy	Accuracy (95% CI, Clopper–Pearson)	Sensitivity (95% CI, Clopper–Pearson)	Specificity (95% CI, Clopper–Pearson)
locked score	Youden-optimal on training donors prevalence-matched (fixed 1 − 4/13 quantile of all training donors)	4	0	1	9	0.9286	1	0.9	0.95	**(0.661-0.998)**	**(0.398-1.000)**	**(0.555-0.997)**
locked score		4	0	1	9	0.9286	1	0.9	0.95	**(0.661-0.998)**	**(0.398-1.000)**	**(0.555-0.997)**
nested selection	median of training negatives (primary)	4	0	7	3	0.5	1	0.3	0.65	**(0.230-0.770)**	**(0.398-1.000)**	**(0.067-0.652)**
nested selection	75th percentile of training negatives	3	1	5	5	0.5714	0.75	0.5	0.625	**(0.289-0.823)**	**(0.194-0.994)**	**(0.187-0.813)**
nested selection	90th percentile of training negatives	3	1	3	7	0.7143	0.75	0.7	0.725	**(0.419-0.916)**	**(0.194-0.994)**	**(0.348-0.933)**
nested selection	Youden-optimal on training donors prevalence-matched (fixed 1 − 4/13 quantile of all training donors)	1	3	1	9	0.7143	0.25	0.9	0.575	**(0.419-0.916)**	**(0.006-0.806)**	**(0.555-0.997)**
nested selection		3	1	1	9	0.8571	0.75	0.9	0.825	**(0.572-0.982)**	**(0.194-0.994)**	**(0.555-0.997)**

Supplementary Table S28. Donor-aware association testing of the WGCNA modules.

The network is the published sample-level network (5,000 genes, seed 42, 23 modules); module eigengenes were averaged within donor (n = 14 independent donors) and correlated with the donor-level Myo+SD+ phenotype. P values are exhaustive: all C(14,4) = 1,001 donor-label assignments were enumerated, with the three replicates kept with their donor. r_sample is the published sample-level correlation, given for comparison. FDR is Benjamini–Hochberg across the 23 modules.

Module	n genes	r (sample level, n = 42)	r (donor level, n = 14)	Permutation P	FDR (23 modules)
blue	1012	0.6555	0.7643	0.004	0.0322
turquoise	1436	-0.6331	-0.7487	0.004	0.0322
cyan	73	-0.5705	-0.6731	0.006	0.0322
lightgreen	63	0.5125	0.6706	0.006	0.0322
red	181	0.5169	0.6455	0.007	0.0322
black	147	0.4405	0.6018	0.018	0.069
yellow	285	0.4092	0.4854	0.0779	0.2502
midnightblue	69	0.3724	0.4749	0.0899	0.2502
green	199	-0.3736	-0.4451	0.0979	0.2502
magenta	127	0.3306	0.4226	0.1219	0.2804
lightcyan	68	-0.3119	-0.3623	0.2098	0.4366
brown	514	-0.242	-0.3481	0.2278	0.4366
darkgreen	36	0.2343	0.2835	0.3217	0.5347
grey60	67	-0.2134	-0.2818	0.3367	0.5347
tan	99	0.2616	0.2762	0.3487	0.5347
salmon	75	0.1742	0.2015	0.4955	0.7123
darkturquoise	33	0.0982	0.1525	0.6034	0.8164
darkred	47	0.0855	0.1231	0.6713	0.8453
royalblue	49	0.0896	0.1127	0.6983	0.8453
purple	119	-0.0757	-0.0909	0.7562	0.8696
greenyellow	112	0.0568	0.0718	0.8052	0.8819
pink	134	-0.0277	-0.0378	0.8981	0.9389
lightyellow	55	0.0106	0.016	0.957	0.957

Supplementary Table S29. Donor-level co-expression of the 15-gene panel after group adjustment.

Raw statistics are the published direction-aware mean pairwise Spearman correlations; adjusted statistics are partial Spearman correlations after regressing each gene on

the four-group factor; within-group statistics average the pairwise correlations computed inside each group. P values come from 10,000 random gene sets drawn from the same mean-expression decile, with the same statistic (including the group adjustment) recomputed. The second block gives the correlation between each gene and the direction-weighted score formed from the other 14 genes (leave-one-gene-out).

Statistic	Observed	Null mean	Null SD	Permutation P
r_up_raw	0.4619	0.0269	0.0827	2e-04
r_down_raw	0.6564	0.0077	0.0702	1e-04
r_cross_raw	-0.4385	0.0155	0.0518	1e-04
r_up_adj	0.263	0.029	0.0868	0.0158
r_down_adj	0.3725	0.0063	0.0682	3e-04
r_cross_adj	-0.1216	0.0147	0.0519	0.0334
r_up_within	0.1519	0.0595	0.2209	0.49
r_down_within	0.7072	0.0114	0.181	6e-04
r_cross_within	-0.1823	0.0331	0.1393	0.19

Gene	Arm	rho with score excluding that gene	P
PAEP	up	0.8857	0
VAT1L	down	-0.8681	7.57e-06
CNTN1	down	-0.8286	0.000397
AL049629.2	up	0.8242	0.000466
RGS7BP	down	-0.7626	0.00231
SMOC2	down	-0.7407	0.00353
COL10A1	down	-0.6923	0.00785
TMEM130	down	-0.6923	0.00785
GAL	up	0.6835	0.00894
SPECC1L-ADORA2A	down	-0.6835	0.00894
PRSS3	up	0.6791	0.00953
MTRNR2L13	up	0.5429	0.0479
PMCH	up	0.5297	0.0544
COMP	down	-0.5121	0.0641
MUSTN1	up	-0.1341	0.648

Supplementary Table S30. Sensitivity of the SLE blood meta-analysis to inclusion of GSE81622.

The prespecified primary analysis uses four cohorts (GSE50772, GSE61635, GSE72326, GSE65391); GSE81622 (30 SLE, 25 control samples, whole blood, GPL10558) was not part of that set and is added here post hoc. Effects are Hedges' g from signed ssGSEA computed with the group labels supplied in external/group_labels; the pooled estimate is a random-effects (REML) meta-analysis.

Dataset	N SLE	N control	Hedges' g	SE
GSE50772	61	20	0.078	0.2553
GSE81622	30	25	0.124	0.2672
GSE61635	99	30	-1.079	0.2177
GSE72326	157	20	-0.43	0.2375
GSE65391	924	72	0.082	0.1223

Five-cohort pooled estimate: g = −0.245 (95% CI −0.703 to 0.213), p = 0.294, I^2 = 84.0%. Four-cohort primary estimate: g = −0.330 (95% CI −0.872 to 0.212), p = 0.232, I^2 = 87.4%. Neither is significant and the conclusion is unchanged.

Supplementary Table S31. Per-fold cut-off values for the five cut-off rules and held-out predictions of the prevalence-matched rule (feature selection repeated inside each leave-one-donor-out fold). One call is decided by a narrow margin: in fold 3 the held-out score (−0.408541) exceeds the median-rule threshold (−0.408977) by 0.000436 on the z scale, so that single call should be read as borderline.

Fold (held-out donor)	Held-out group	Training positive donors	Genes selected	θ median (non-Myo+SD+)	θ 75th percentile	θ 90th percentile	θ Youden-optimal	θ prevalence	Held-out score	Called positive (prevalence-matched rule)
1	HC	4	14	-0.3835	-0.220157	0.07425	0.54563	0.598706	-0.144492	**No**
2	HC	4	8	-0.399157	-0.228129	0.010248	-0.103354	0.433752	-1.001017	**No**
3	HC	4	13	-0.408977	-0.237817	-0.010182	0.462174	0.500011	-0.408541	**No**
4	Myo−	4	13	-0.362091	-0.139898	0.008801	0.560304	0.599977	-0.244759	**No**
5	Myo−	4	15	-0.359087	-0.294796	-0.002435	0.563744	0.610747	-0.893747	**No**

Fold (held-out donor)	Held-out group	Training positive donors	Genes selected	θ median (non-Myo+SD+)	θ 75th percentile	θ 90th percentile	θ Youden-optimal	θ prevalence	Held-out score	Called positive (prevalence-matched rule)
6	Myo−	4	12	-0.386322	-0.217992	-0.010137	0.522387	0.563854	-0.085222	**No**
7	Myo+SD−	4	6	-0.388298	-0.226541	0.033353	-0.18926	0.47191	-0.53017	**No**
8	Myo+SD−	4	6	-0.378836	-0.200231	-0.064709	0.348842	0.494497	0.069883	**No**
9	Myo+SD−	4	61	-0.375585	-0.292986	-0.162763	0.02995	0.196248	1.395576	**Yes**
10	Myo+SD−	4	12	-0.496087	-0.302777	-0.067755	0.29503	0.336152	0.233903	**No**
11	Myo+SD+	3	69	-0.339383	-0.248739	-0.014608	0.264429	0.049785	0.095112	**Yes**
12	Myo+SD+	3	2	-0.33655	-0.038646	0.053766	0.49137	0.154751	0.983987	**Yes**
13	Myo+SD+	3	32	-0.299357	0.130112	0.211756	0.590938	0.299259	0.074845	**No**
14	Myo+SD+	3	12	-0.333194	-0.174346	0.100584	0.718502	0.24318	0.585199	**Yes**

θ prevalence is the (1 − 4/13) quantile of the z-scores of all 13 training donors (positive and negative pooled), evaluated with the default type-7 quantile; 4/13 is a fixed constant and does not change when the held-out donor is itself Myo+SD+. In folds 11–14 the training set therefore contains only three Myo+SD+ donors while the rule still places roughly four of the 13 training donors above the cut-off, so at least one negative donor is called positive by construction; the same holds for the locked-score block of Table S27, which uses the identical fixed quantile. Observed under this rule: TP = 3, FN = 1 (fold 13, score 0.0748 < θ 0.2993), FP = 1 (fold 9, score 1.3956 > θ 0.1962), TN = 9. θ varies across folds from 0.0498 to 0.6107 on the z scale. Two implementation details qualify these numbers. First, the gene-level detection prefilter (at least 10 counts in at least 3 samples) was applied once to all 42 samples and was not recomputed inside each training set; recomputing it within the training data leaves the prevalence-matched result unchanged (TP 3, FN 1, FP 1, TN 9) but changes the median-rule accuracy from 7/14 to 8/14 and the Youden-optimal accuracy from 10/14 to 11/14. Second, in fold 3 the held-out score exceeds the median-rule threshold by only 0.000436, so that single call is borderline.