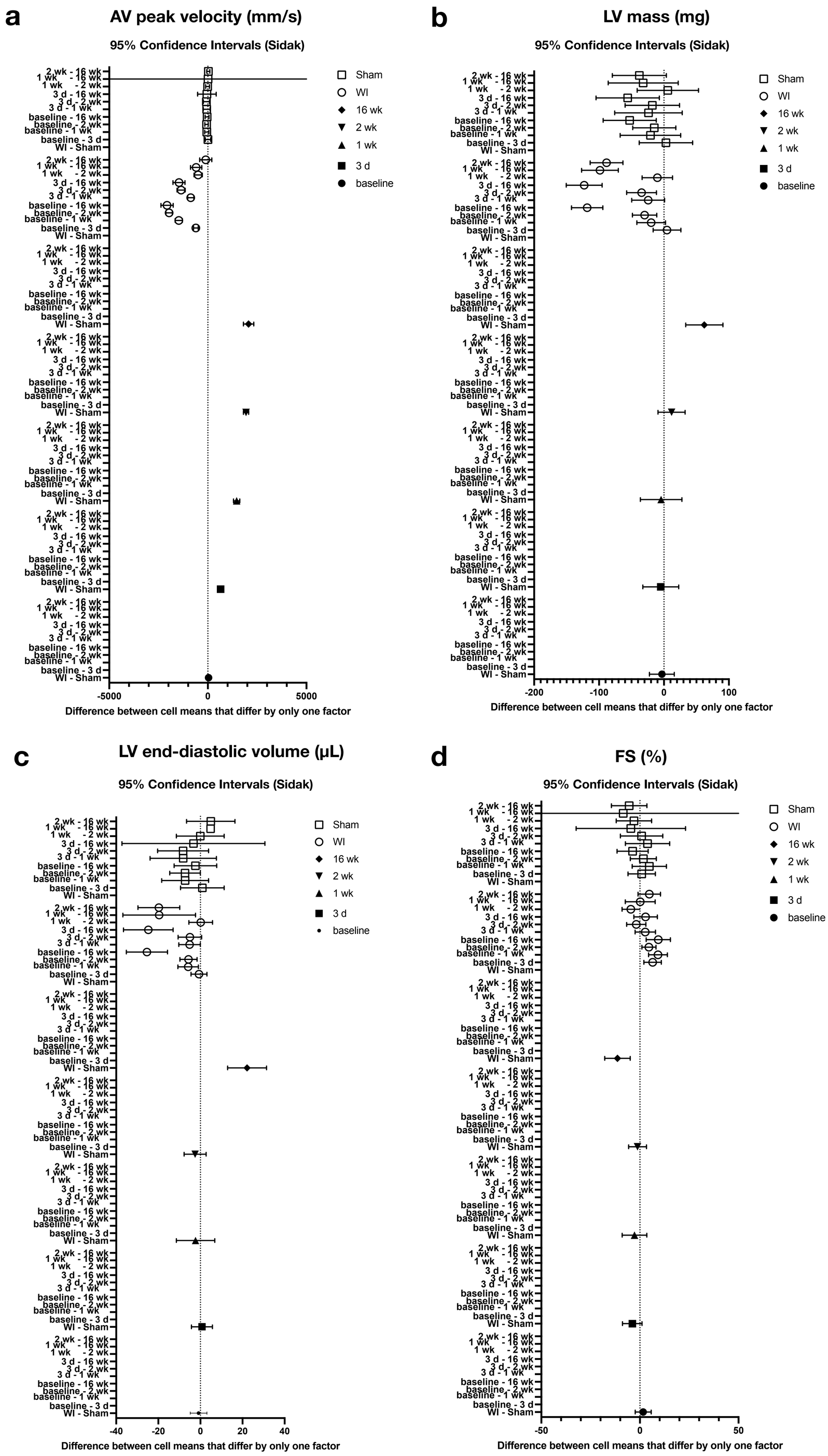
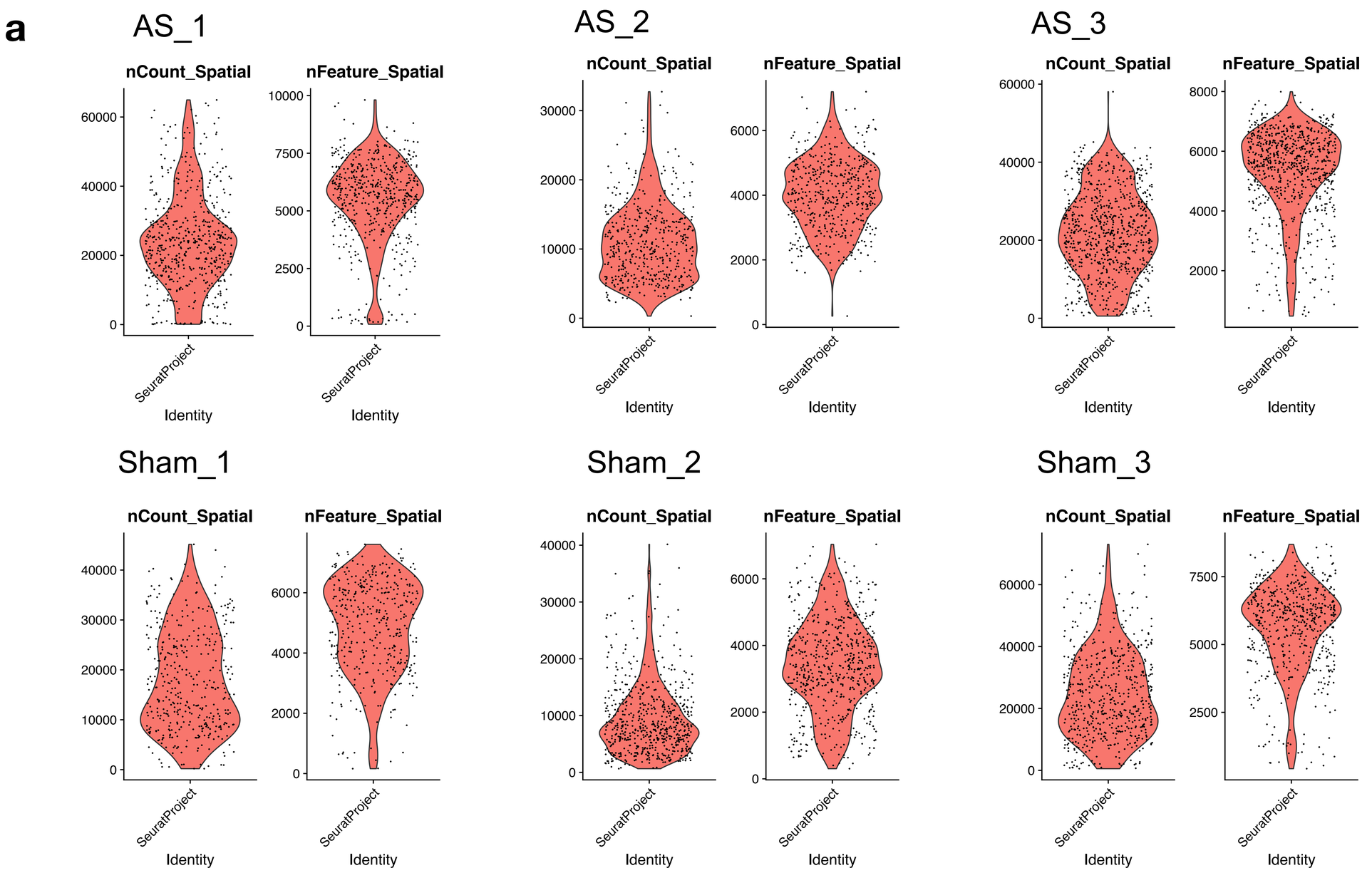
Supplementary Fig. 1

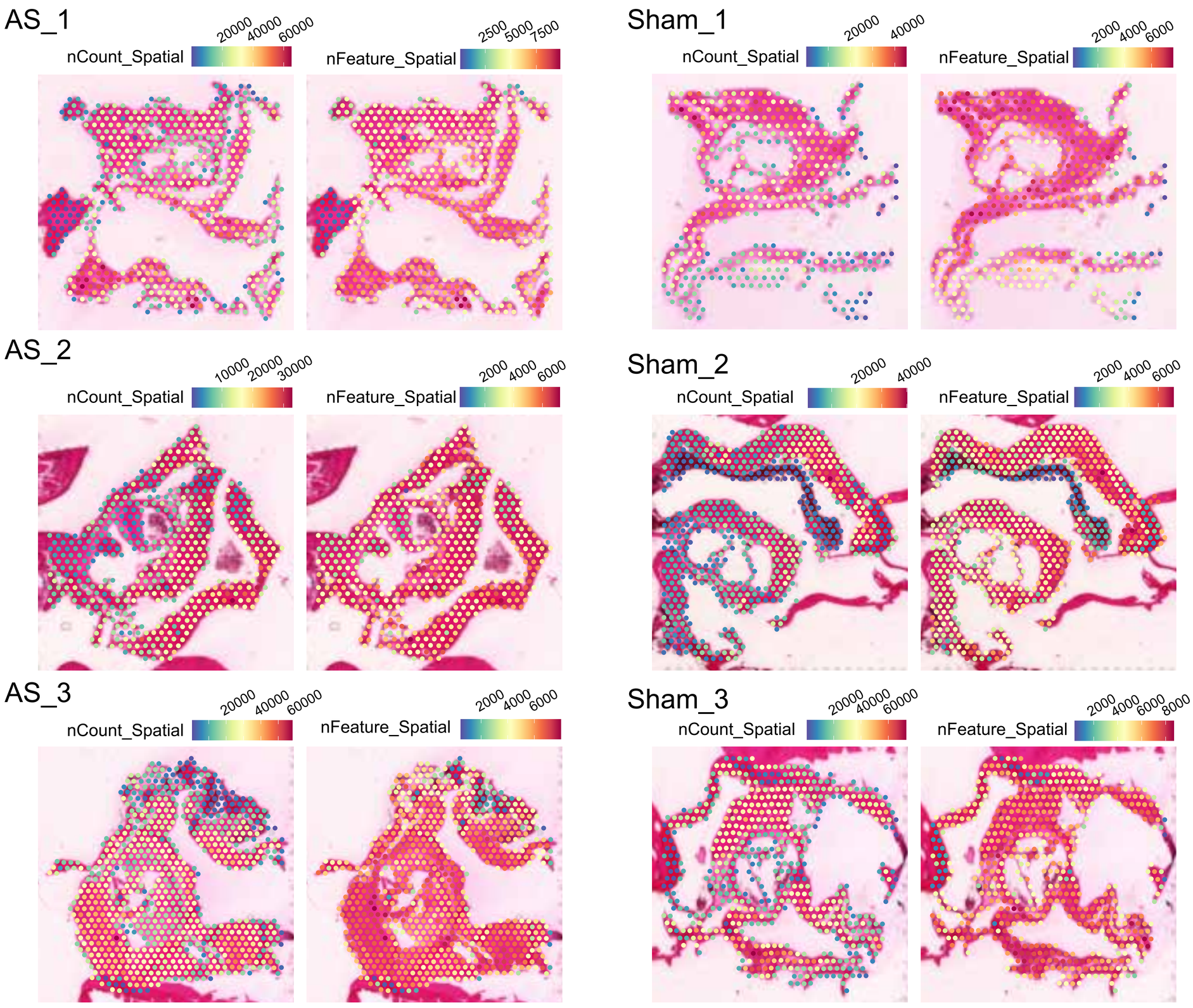


Supplementary Fig. 1 | Post hoc pairwise comparison data from serial TTE measurement after WI procedure in the wild-type mice group.

a–d Sidak-adjusted post-hoc comparisons of AV peak velocity (**a**), LV mass (**b**), LV end-diastolic volume (**c**), and FS (**d**) after two-way ANOVA. Symbols indicate mean differences, horizontal bars indicate 95% confidence intervals, and dotted vertical lines indicate no differences. AV, aortic valve; LV, left ventricular; FS, fractional shortening (%); ANOVA, analysis of variance; CI, confidence interval; d, day; wk, week; WI, wire injury.

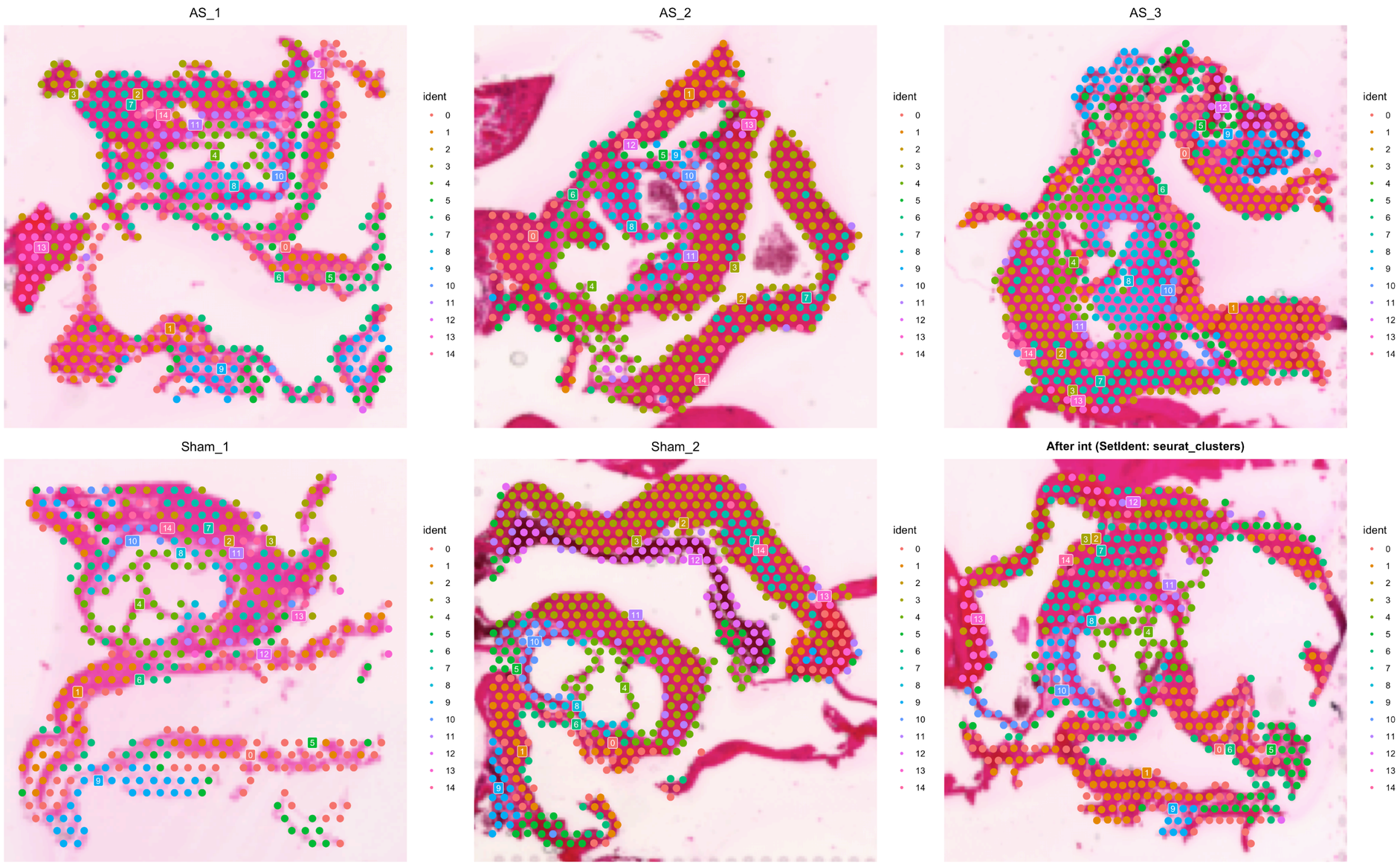
Supplementary Fig. 2





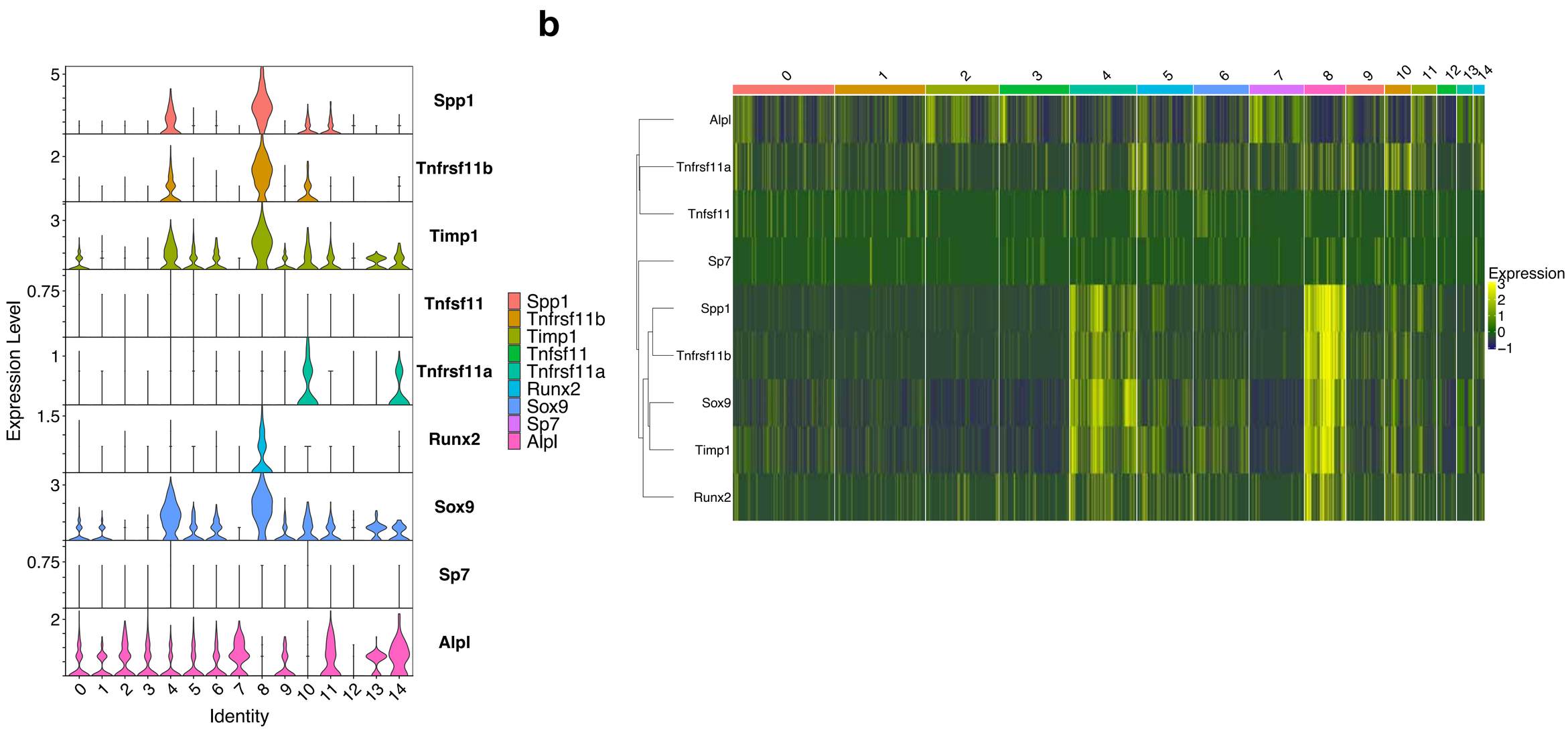
Supplementary Fig. 2 | Quality control of Visium spatial transcriptomic datasets from aortic valve sections containing adjacent tissue in a mouse model of early-stage AS/CAVD.
a, Violin plots showing the distribution of total unique molecular identifier (UMI) counts per spot (nCount_Spatial) and the number of detected genes per spot (nFeature_Spatial) for each Visium sample. The dots represent individual Visium spots. **b** Spatial feature plots showing the corresponding spatial distribution of QC metrics across tissue sections from six specimens. *n* = 6 specimens: AS (*n* =3) and sham (*n* =3).

Supplementary Fig. 3



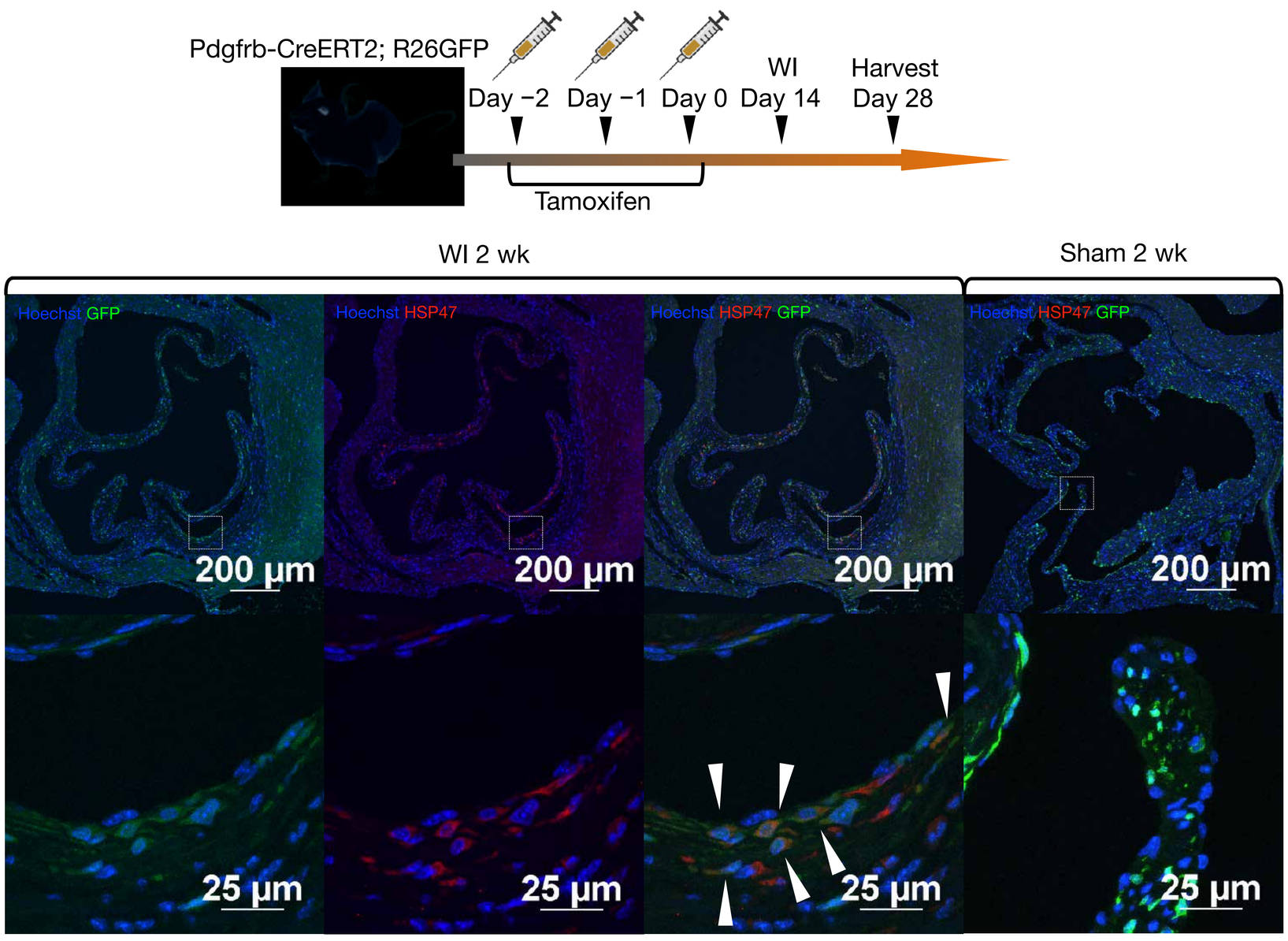
Supplementary Fig. 3 | Principal component selection and spatial clustering of Visium datasets.
a, Elbow plots showing the standard deviation of the principal components for each Visium specimen. **b**) Spatial cluster maps showing the distribution of unsupervised spot clusters across tissue sections for each specimen. *n* = 6 specimens, including AS, *n* =3, and sham, *n* =3.

Supplementary Fig. 4



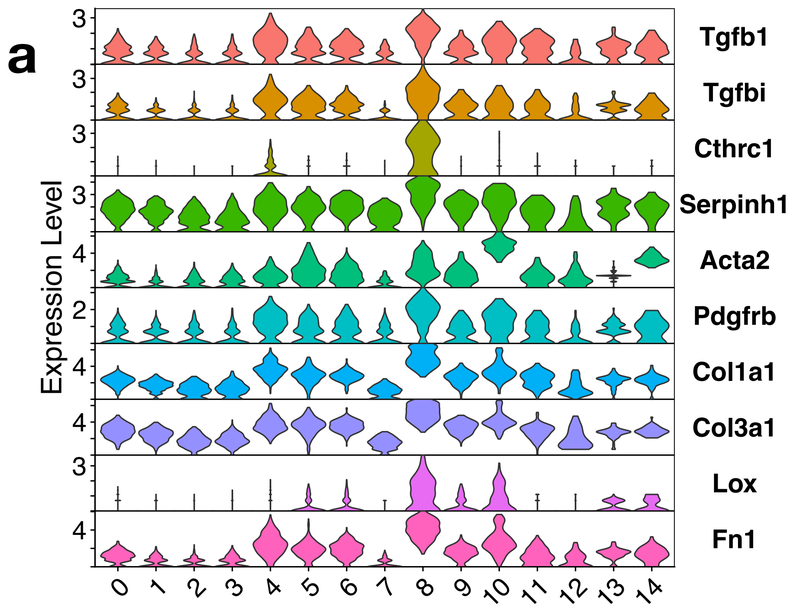
Supplementary Fig. 4 | Spatial osteochondrogenesis-related gene expression in early-stage CAVD/AS.
a, Violin plots of osteochondrogenesis-related gene signatures. **b,** Heat map of the same gene panel across Visium clusters 0–14; color denotes gene-wise scaled expression (z-score). The row dendrogram shows the unsupervised hierarchical clustering of genes. Key clusters: 4, healthy leaflet tissue; 8, stenotic leaflet tissue; 10, annulus.

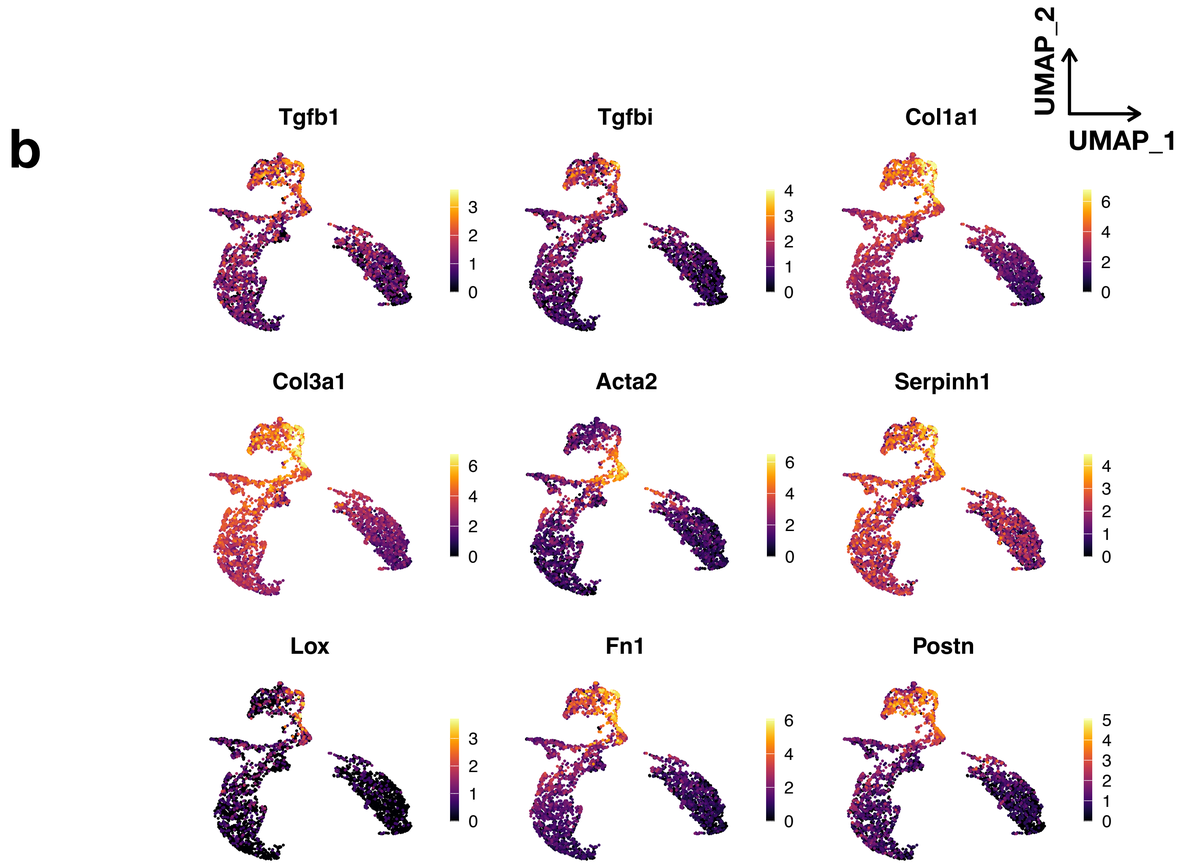
Supplementary Fig. 5

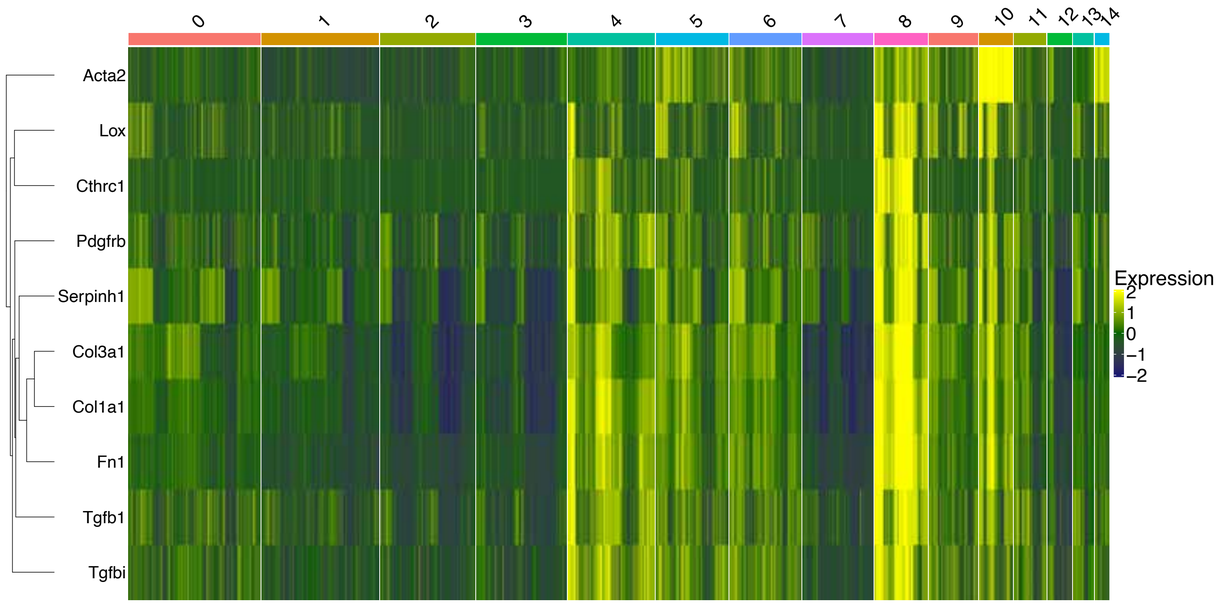


Supplementary Fig. 5 | Linage tracing reveals HSP-47 expression in Pdgfrb-lineage cells following endothelial injury and activation.
Pdgfrb-CreERT2; R26GFP mice were used for lineage tracing. Tamoxifen was administered intraperitoneally at 100 mg kg^{-1} body weight per day for 3 consecutive days. Fourteen days after the final tamoxifen injection, mice underwent the WI, and their hearts were harvested for analysis 14 days later. White arrowheads: cells double-positive for GFP and HSP47. Scale bars, 200 μm (top) and 25 μm (bottom). wk, week.

Supplementary Fig. 6

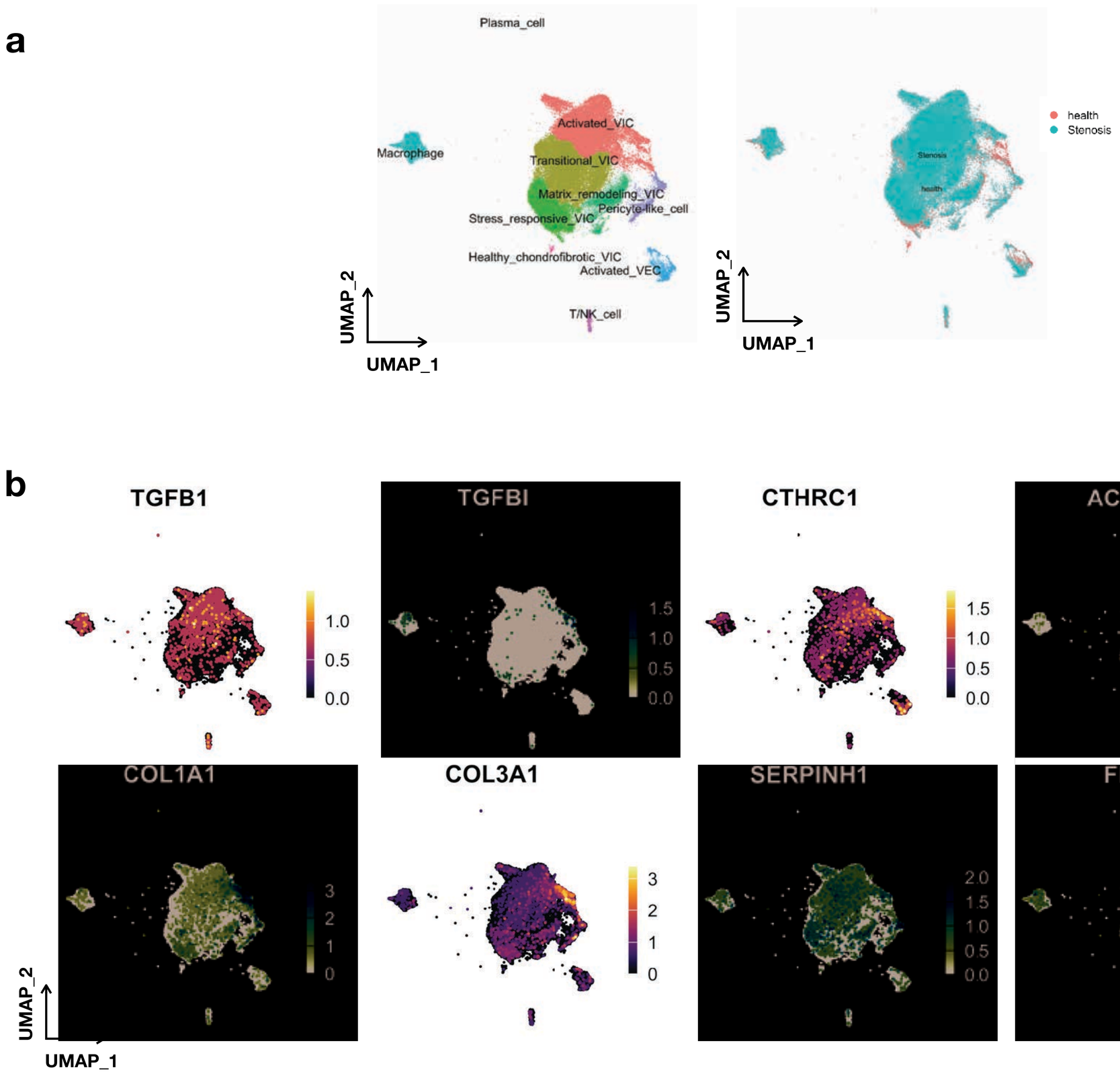






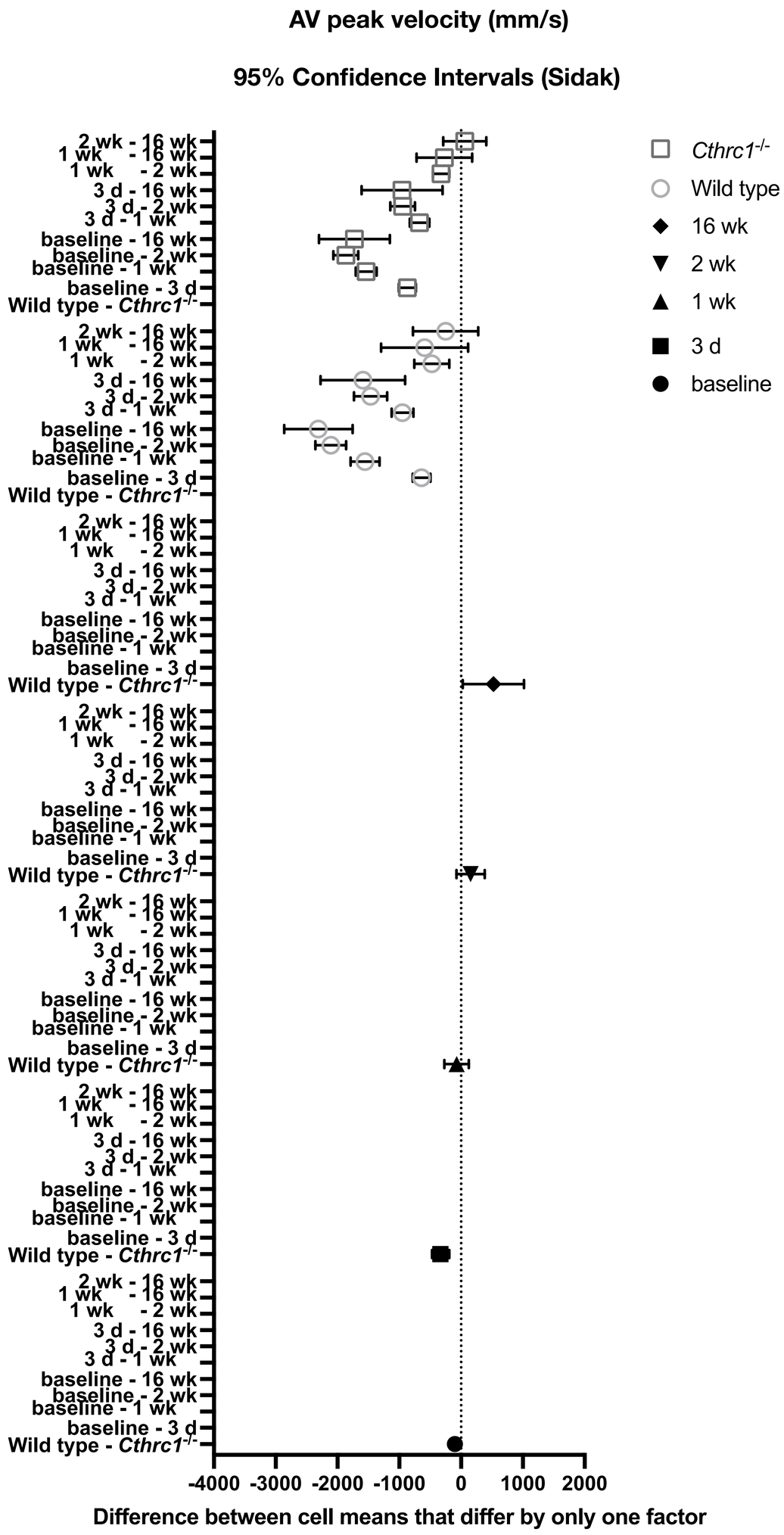
Supplementary Fig. 6 | Spatial fibro-remodeling-related gene expression in early-stage CAVD/AS.
a, Violin plots showing normalized expression per cluster for the same gene panel; cluster identities are shown in Figure 2a. **b**, UMAP with Visium spot-level expression overlays; color indicates normalized expression (scale shown). **c,** Heat map of the same gene panel across Visium clusters 0–14; color denotes gene-wise scaled expression (z-score). The row dendrogram shows the unsupervised hierarchical clustering of genes. Key clusters: 4, healthy leaflet tissue; 8, stenotic leaflet tissue; 10, annulus.

Supplementary Fig. 7



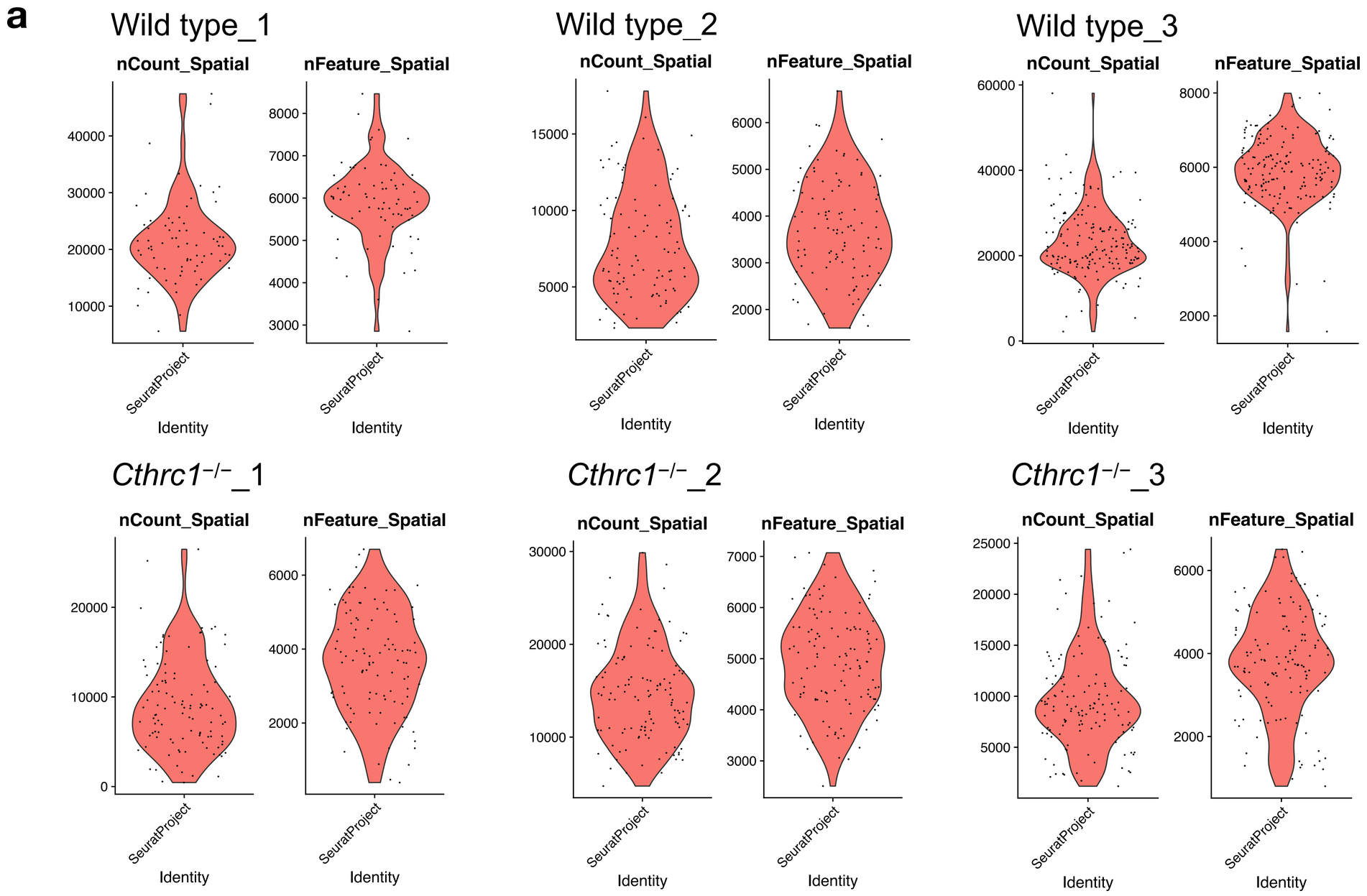
Supplementary Fig. 7 | Reanalysis of public human CAVD/AS scRNA-seq datasets identifies *TGFB1* expression and fibro-remodeling signatures.
a, UMAP visualization of reanalyzed human CAVD/AS and healthy control valve cells with cell type annotations (left) and sample origins (CAVD/AS patient-derived vs. healthy donor-derived cells; right). **b** Feature plots showing the expression of *TGFB1* and genes related to fibro-remodeling across annotated cell populations.

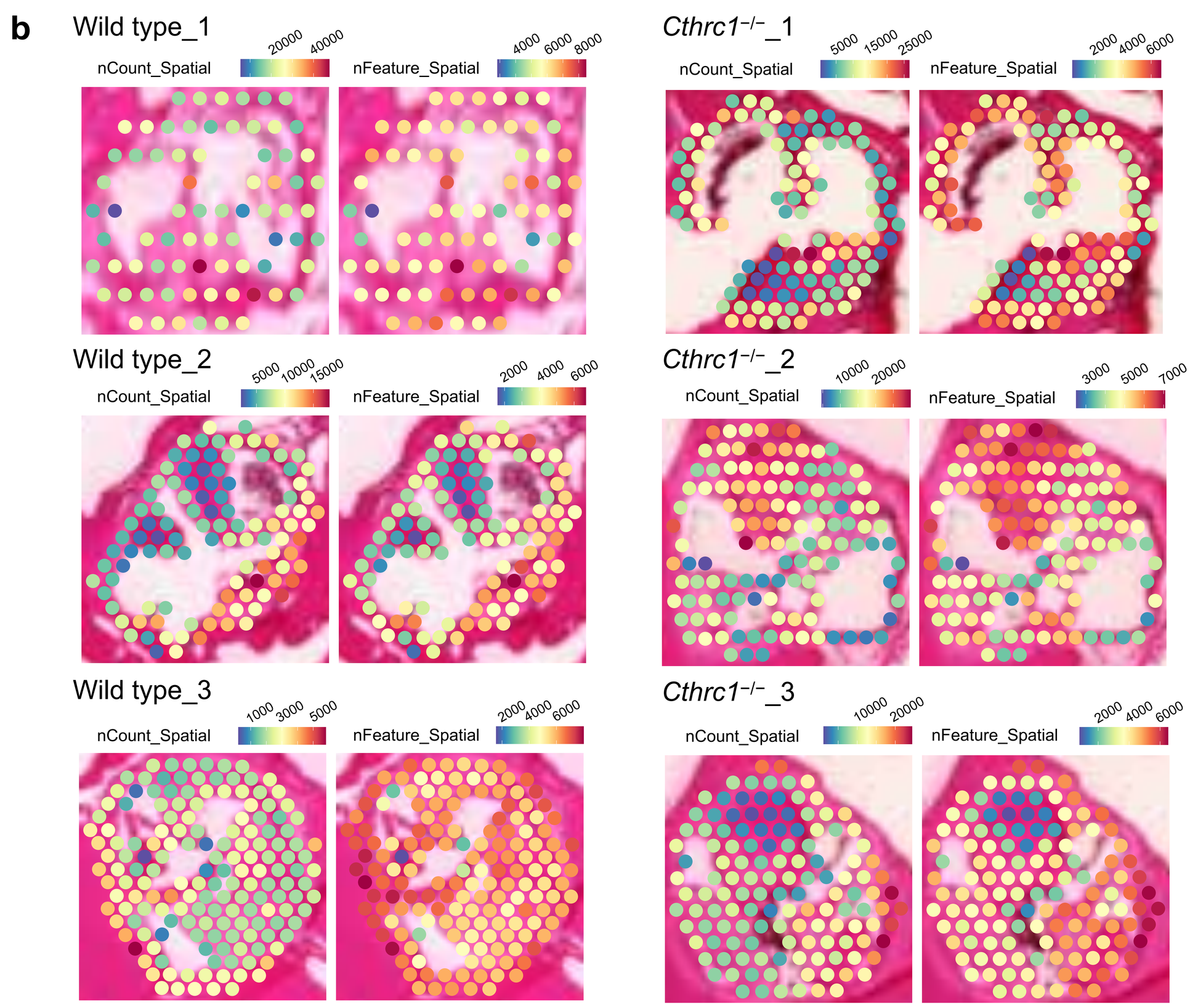
Supplementary Fig. 8



Supplementary Fig. 8 | *Cthrc1* deficiency does not alter hemodynamics in early-stage AS.
Sidak-adjusted post-hoc comparisons of AV peak velocity after two-way ANOVA. Symbols indicate mean differences, horizontal bars indicate 95% confidence intervals, and dotted vertical lines indicate no differences. d, day; wk, week.

Supplementary Fig. 9

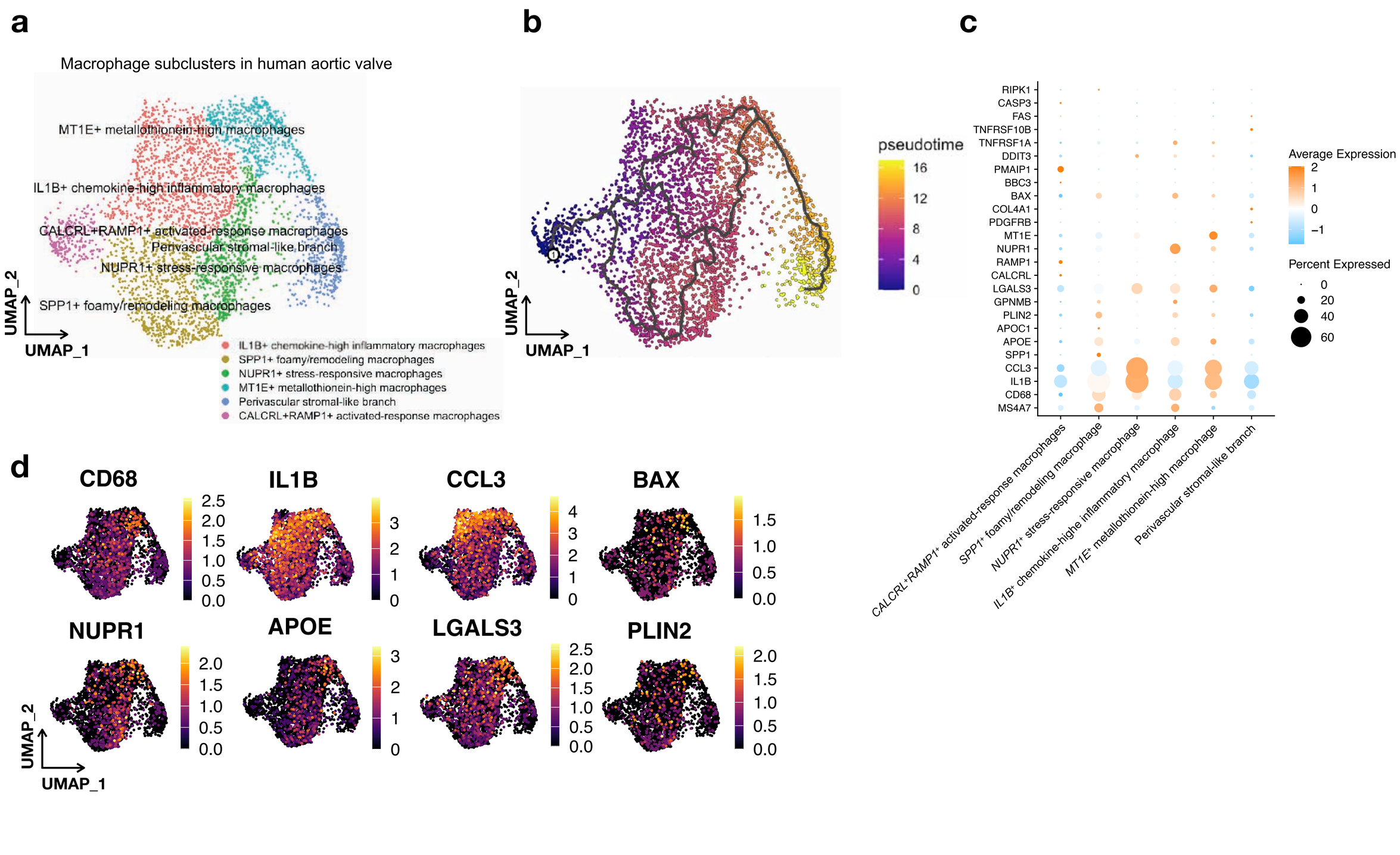




Supplementary Fig. 9 | QC of Visium spatial transcriptomic datasets from aortic valve sections in *Cthrc1*$^{-/-}$ mice with early-stage AS/CAVD.

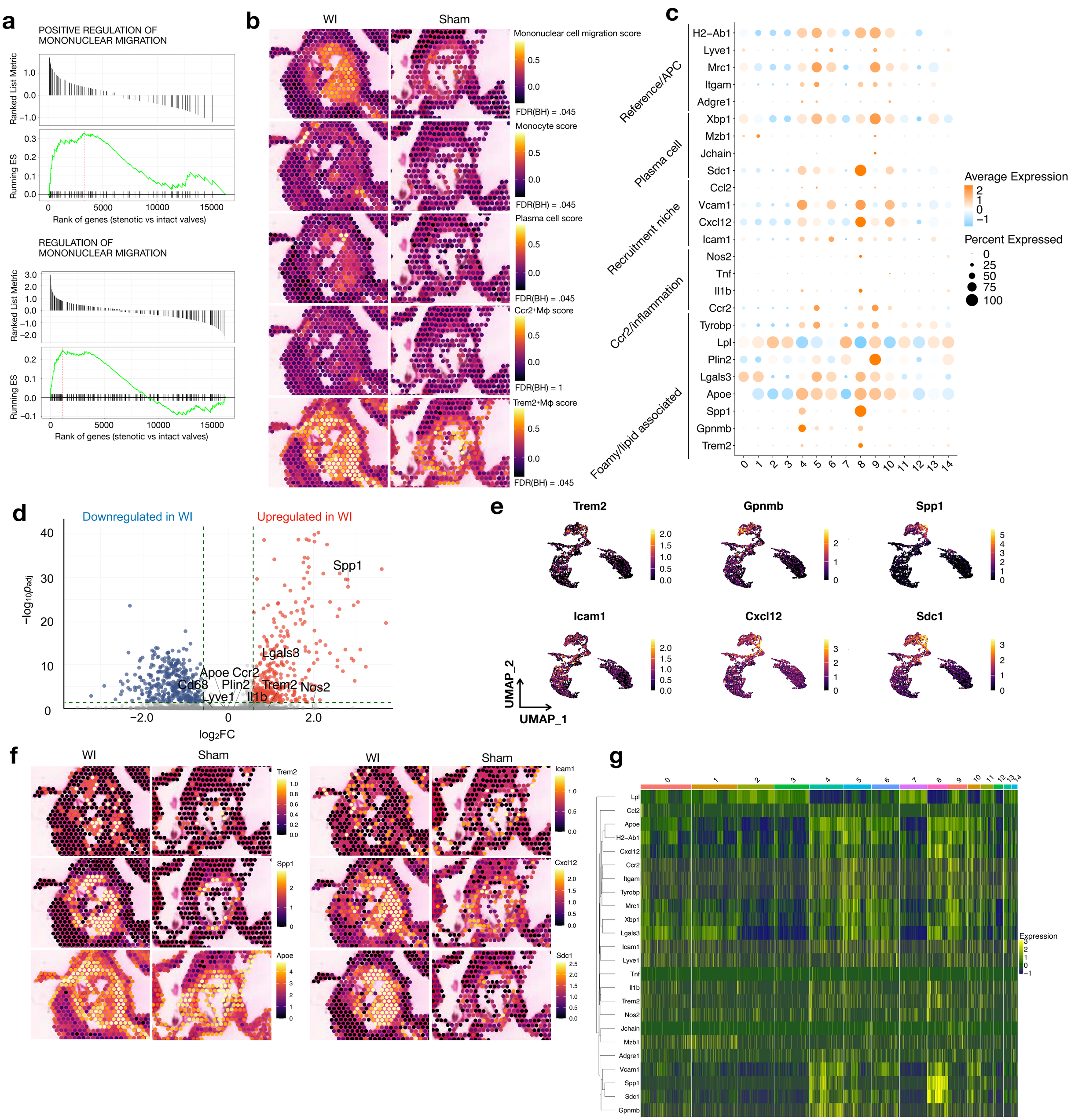
a–b, Visium spots corresponding to the stenotic valve region were manually annotated in the Loupe Browser (v7.0.0) and extracted for downstream analysis. **a**, Violin plots showing the distribution of total UMI counts per spot (nCount_Spatial) and the number of detected genes per spot (nFeature_Spatial) for each Visium sample. The dots represent individual Visium spots. **b** Spatial feature plots showing the corresponding spatial distribution of QC metrics across tissue sections from six specimens. $n = 6$ specimens, including wild type mice with AS, $n = 3$, and *Cthrc1*$^{-/-}$ mice with AS, $n = 3$.

Supplementary Fig.10



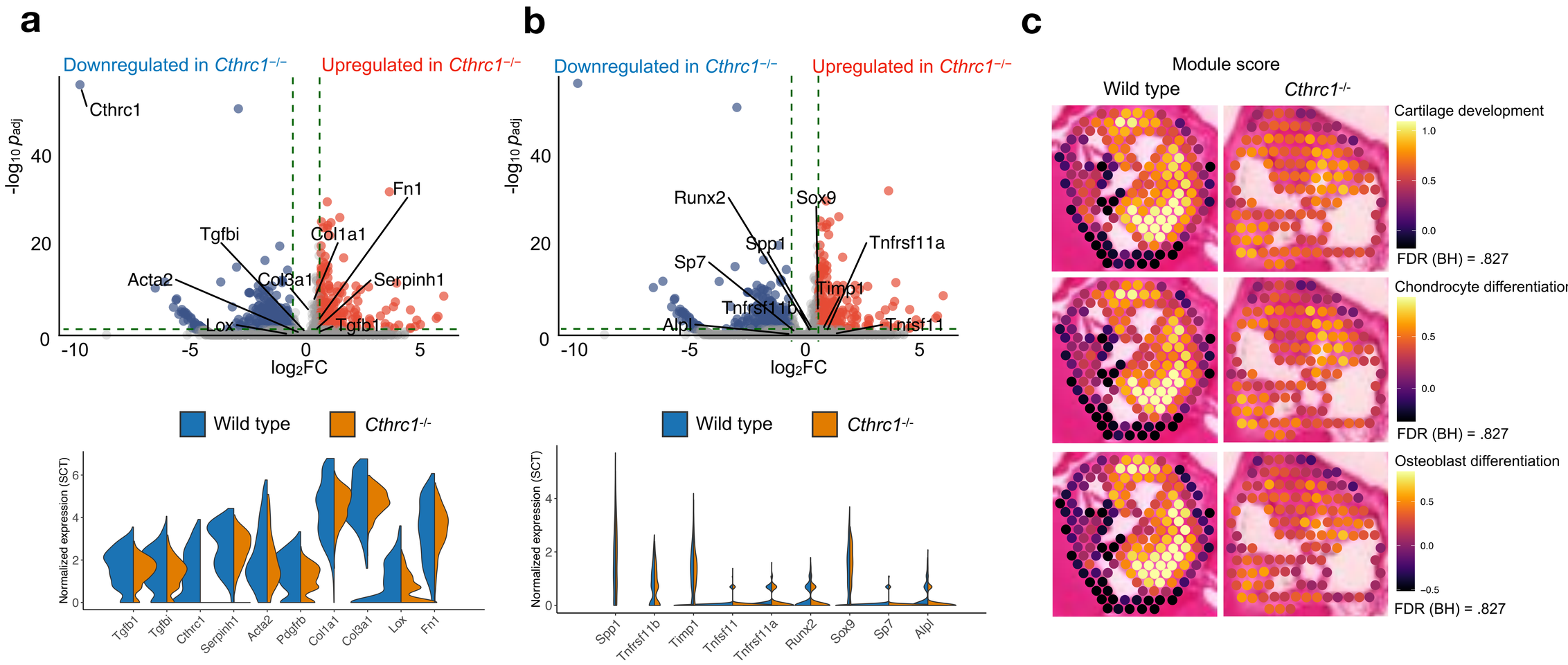
Supplementary Fig. 10 | *LGALS3* and foamy macrophage-related gene expression in macrophage subclusters from public human CAVD scRNA-seq data.
a, UMAP visualization of macrophage subclusters extracted from the reanalyzed public human CAVD scRNA-seq dataset. Subclusters were annotated according to their marker gene expression. **b**, Pseudotime trajectory analysis projected onto the UMAP embedding of macrophage subclusters. The color scale indicates the pseudotime. **c,** Dot plot showing the expression of *LGALS3* and selected foamy macrophage-related genes across the macrophage subclusters. **d,** Feature plots showing the expression of selected genes on the same UMAP embedding used for pseudotime trajectory analysis.

Supplementary Fig.11



Supplementary Fig. 11 | Spatial transcriptome illustrated immune-associated gene expression in early-stage CAVD/AS.
a, GSEA enrichment plots for GO terms positive regulation of mononuclear cell migration and regulation of mononuclear cell migration in stenotic versus healthy leaflet regions. Green curves show the running enrichment score, and tick marks indicate gene hits. **b**, Spatial feature plots of module scores for GOBP term positive regulation of mononuclear cell migration and literature-curated monocyte, plasma cell, *Ccr2*$^{+}$ macrophage, and *Trem2*$^{+}$ macrophage scores. Right, module score and FDR values for each gene set. **c**, Dot plot (dot size = percentage of spots; color = scaled average expression). **d**, Differential expression between stenotic leaflet versus healthy leaflet: x-axis, log2FC; y-axis, −log10 Bonferroni-adjusted *p*-value. Selected immune-associated genes were labeled. **e–f**, Feature plots of fibro-remodeling markers. **e**, UMAP with Visium spot-level expression overlays; color indicates normalized expression (scale shown). **f,** Spatial expression maps across Visium sections encompassing the aortic valve and neighboring myocardium; color indicates normalized expression (scale shown). **g,** Heat map of the fibro-remodeling gene panel across Visium clusters 0–14; color denotes gene-wise scaled expression (z-score). The row dendrogram shows the unsupervised hierarchical clustering of genes. Key clusters: 4, healthy leaflet tissue; 8, stenotic leaflet tissue; 10, annulus. WI, wire injury

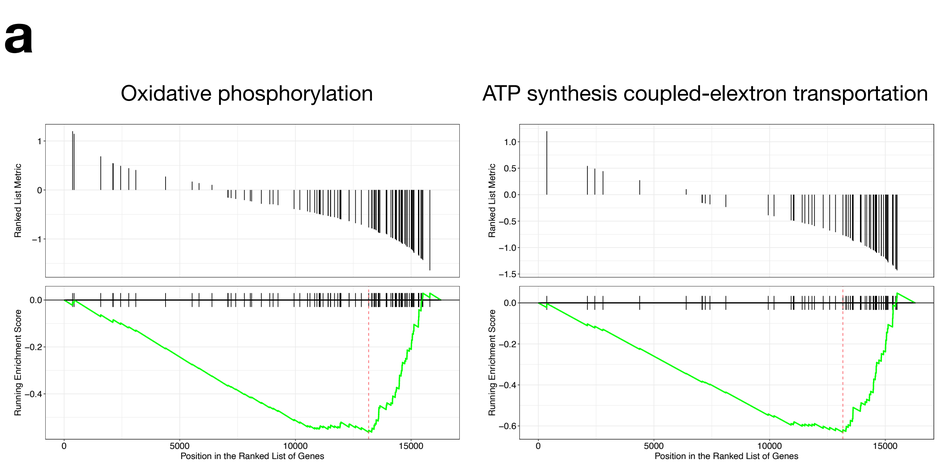
Supplementary Fig.12

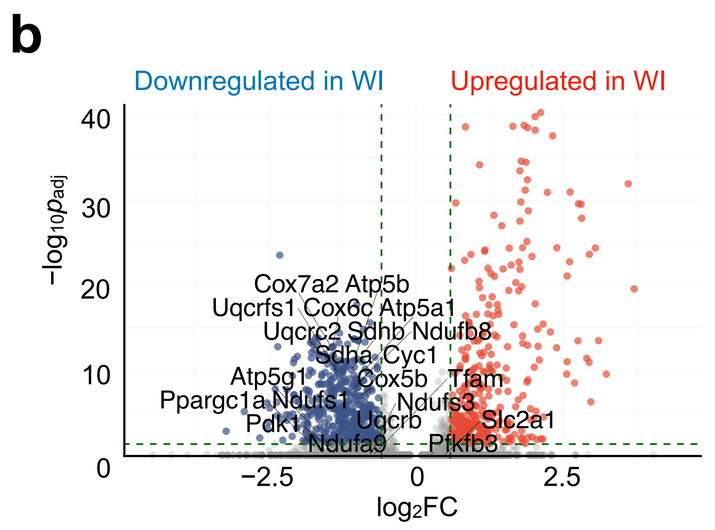


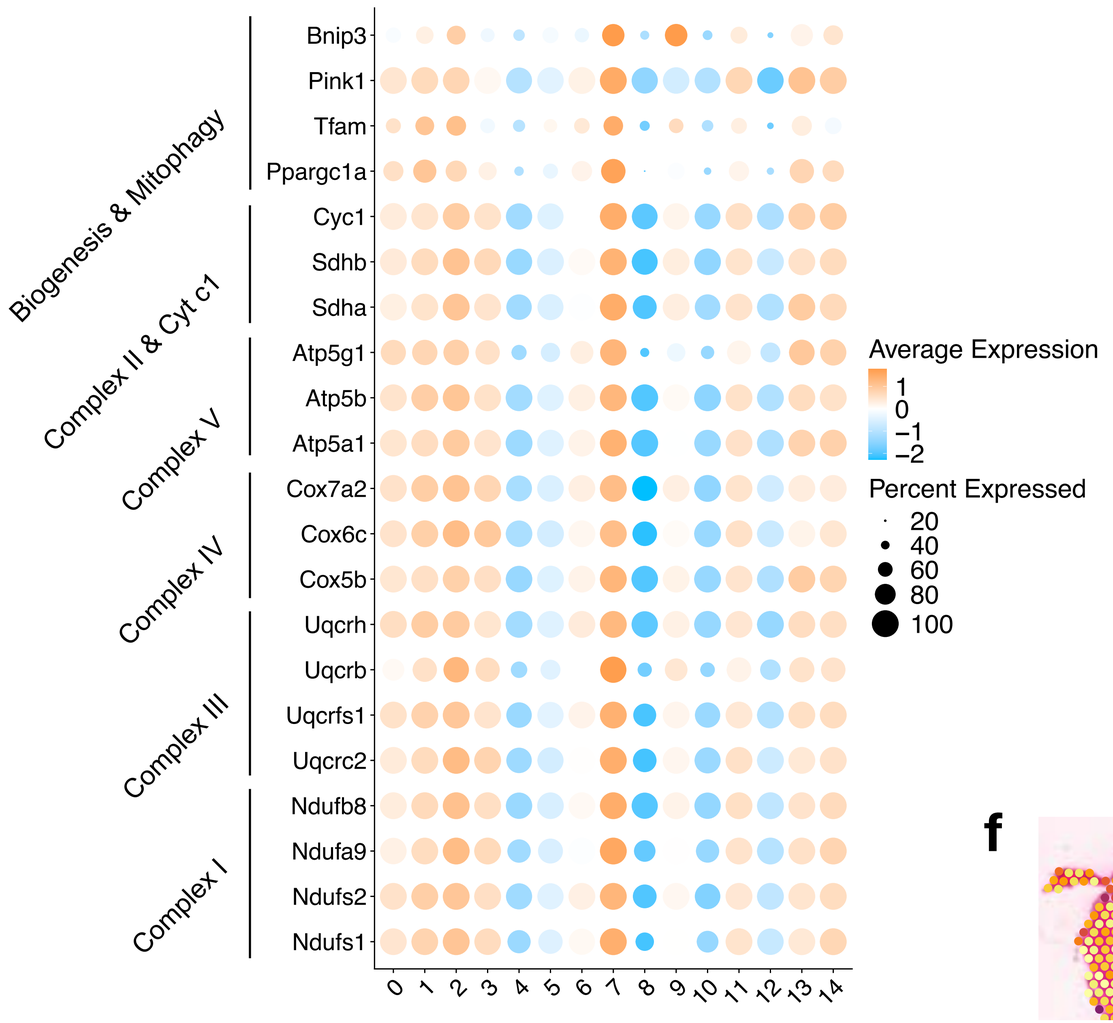
Supplementary Fig. 12 | Expression of osteochondrogenesis- and fibro-remodeling-related genes in stenotic valves under *Cthrc1*-deficient conditions.

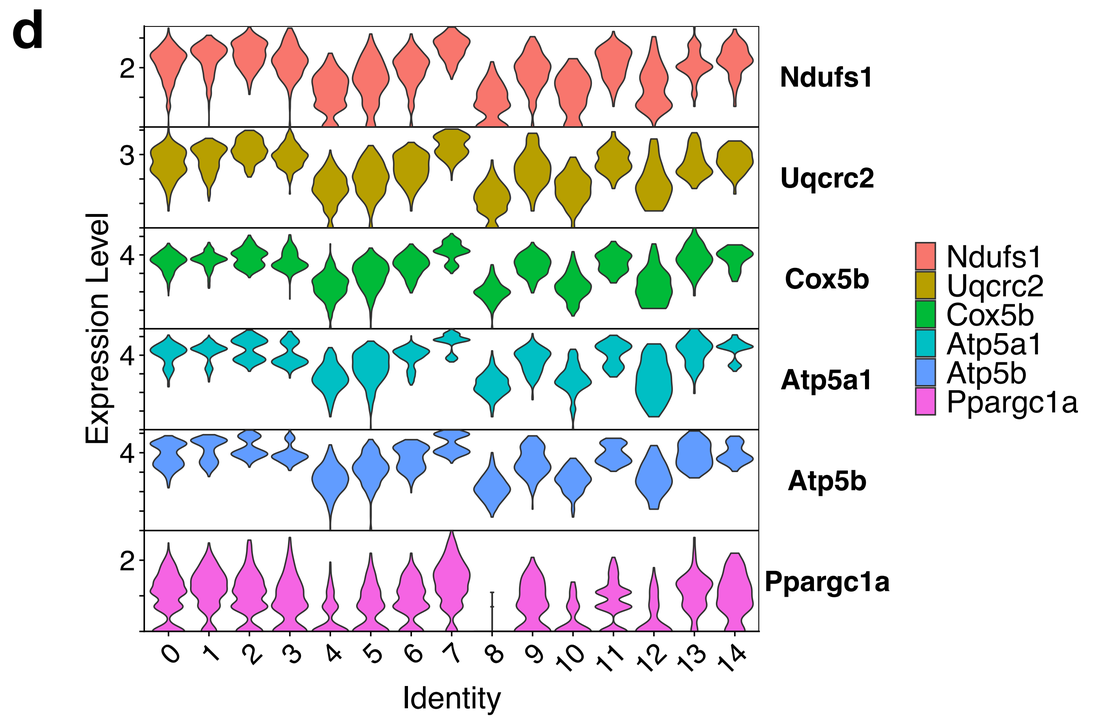
a–b, Differential expression and violin plots showing expression of genes related to fibro-remodeling (**a**) and osteochondrogenesis (**b**) in early-stage CAVD valves from wild-type and *Cthrc1*$^{-/-}$ groups. **c,** Spatial feature plots of module scores for GOBP terms positive regulation of chondrocyte differentiation, positive regulation of cartilage development, and positive regulation of osteoblast differentiation. BH, Benjamini–Hochberg; FDR, false discovery rate.

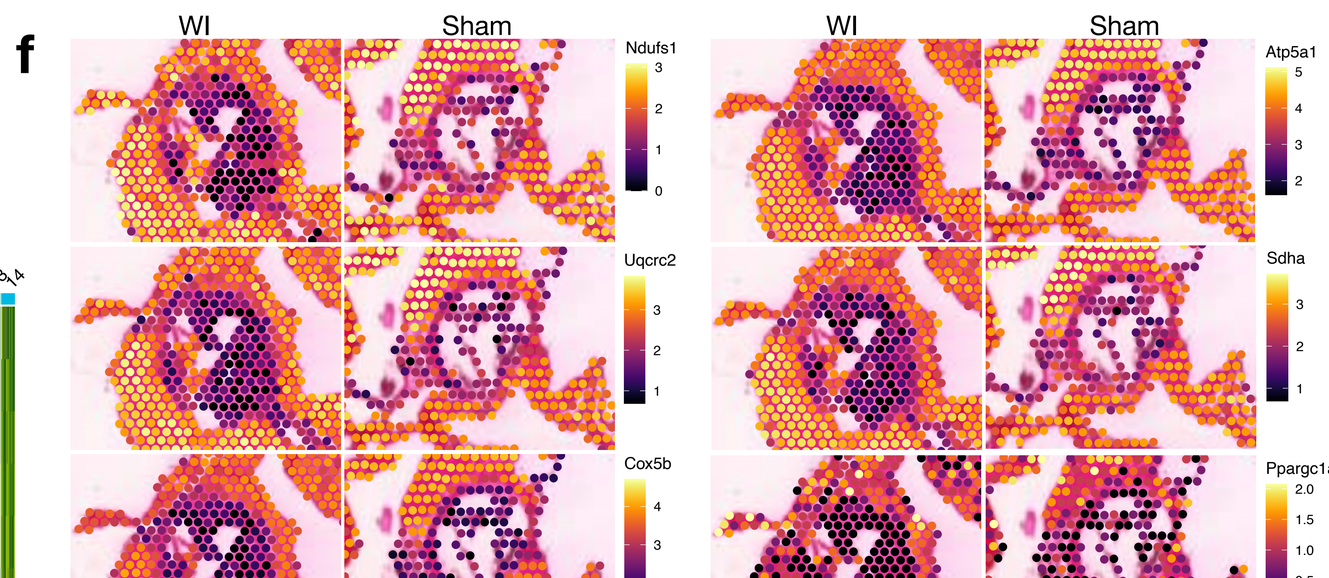
Supplementary Fig.13

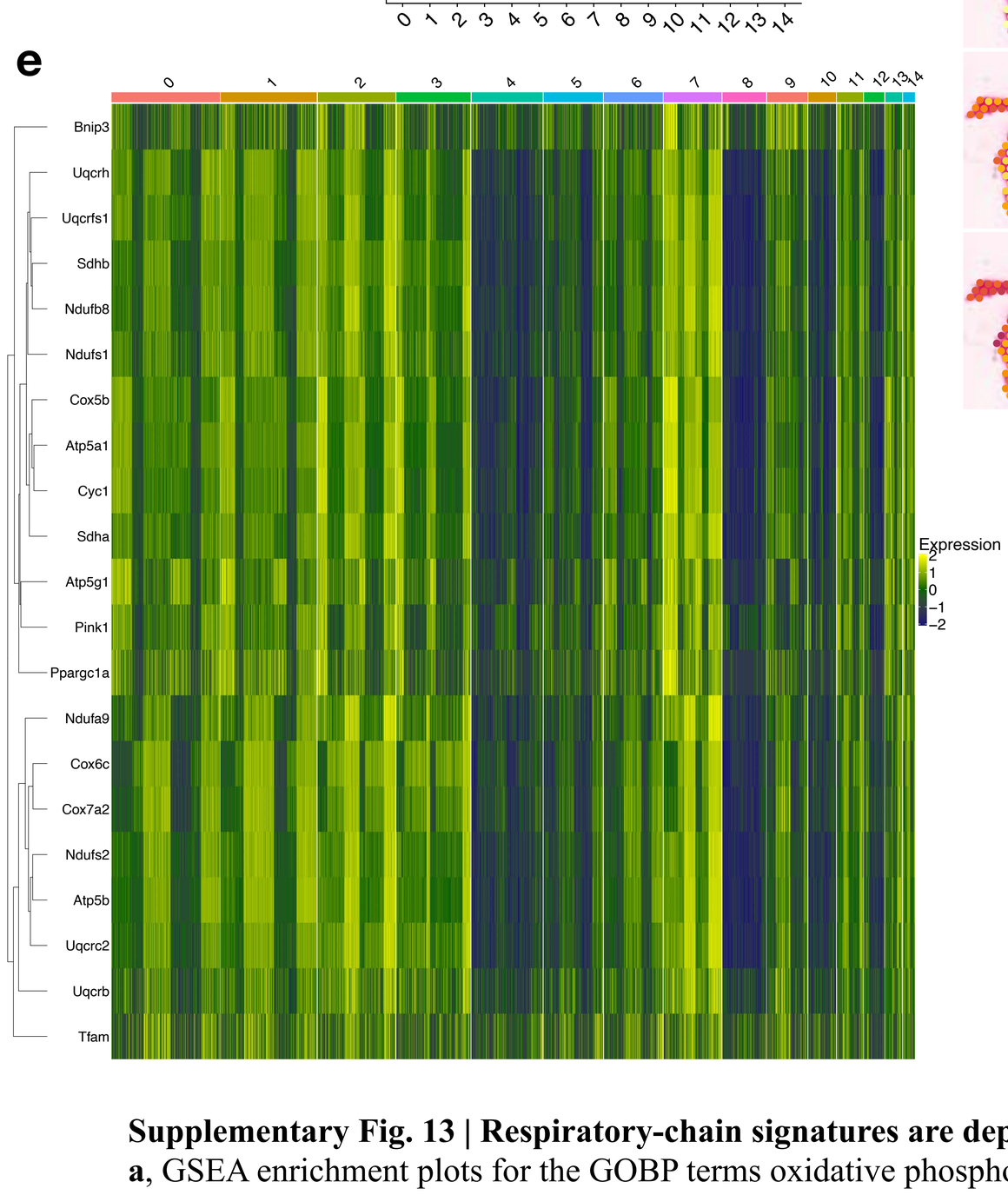


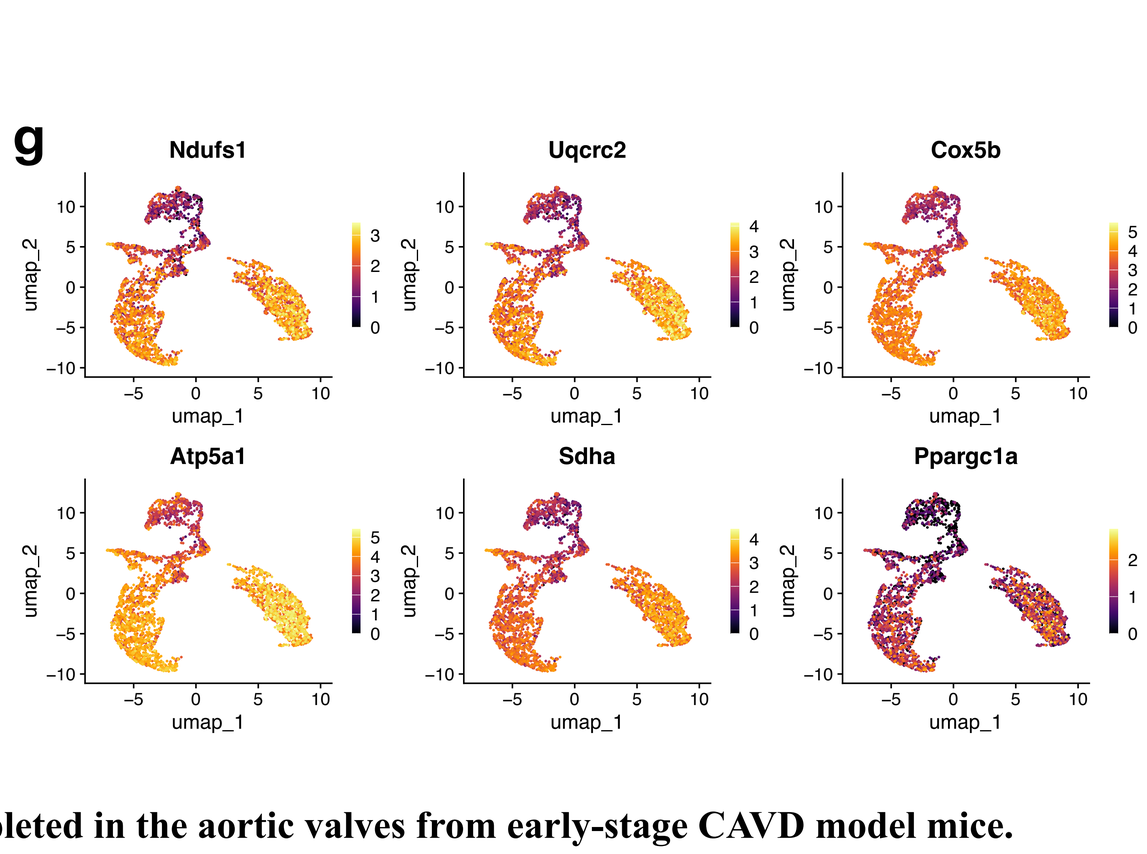






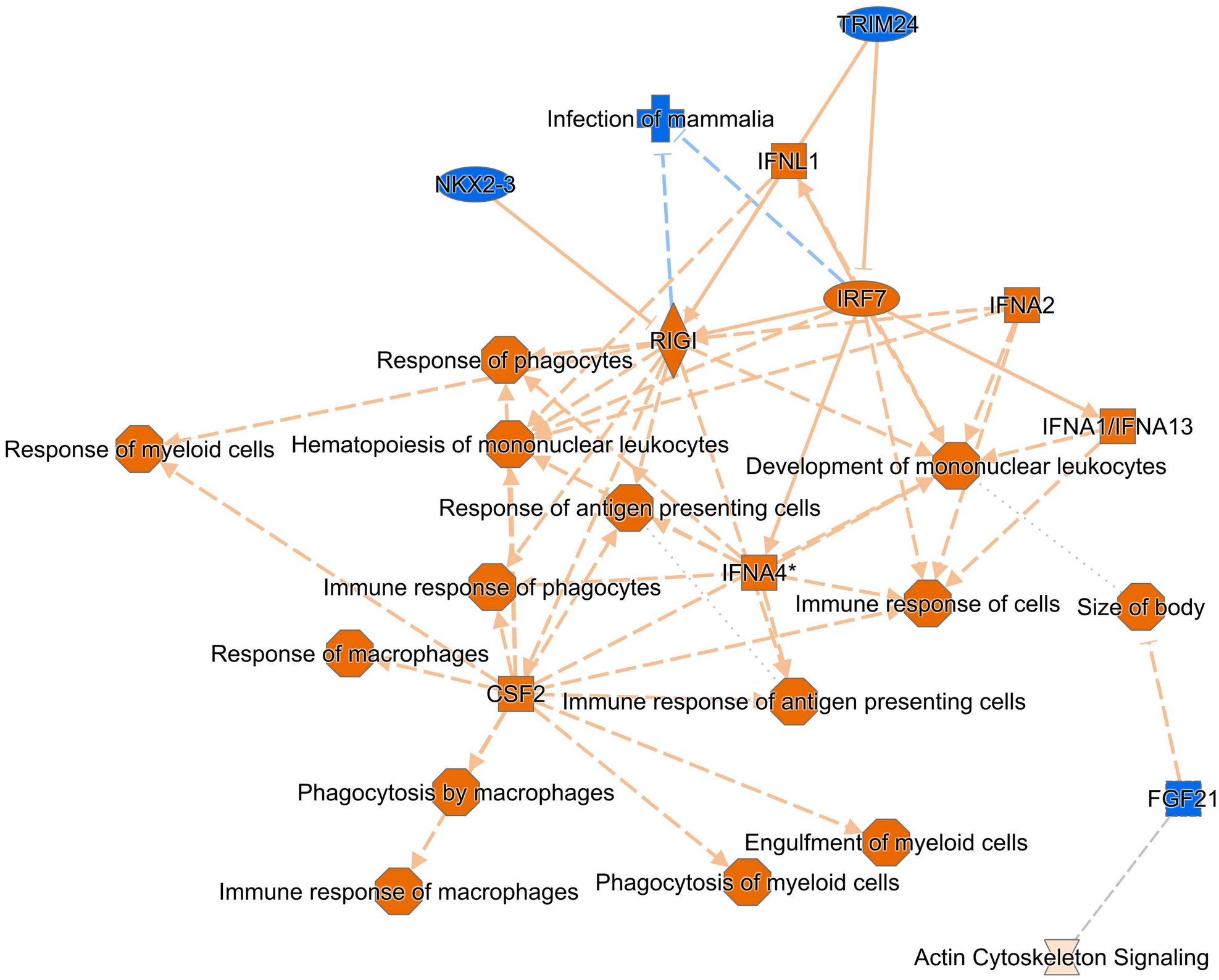






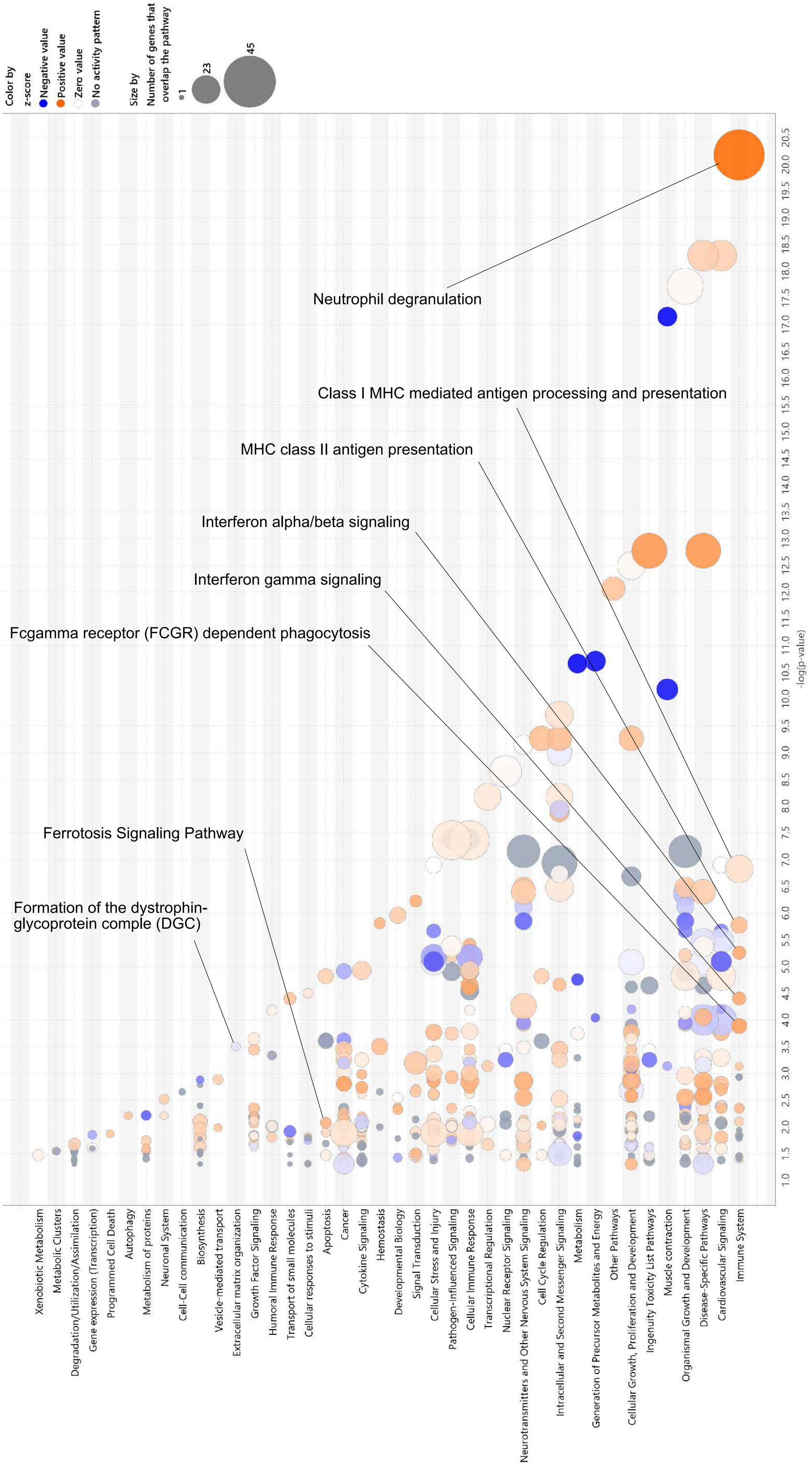
Supplementary Fig. 13 | Respiratory-chain signatures are depleted in the aortic valves from early-stage CAVD model mice. **a**, GSEA enrichment plots for the GOBP terms oxidative phosphorylation and ATP synthesis-coupled electron transport, comparing stenotic valvular regions with healthy leaflet regions from wild-type mice. Green curves show the running enrichment score, and tick marks indicate gene hits. **b**, Differential expression between stenotic versus healthy leaflets: x-axis, log2FC; y-axis, −log10 Bonferroni-adjusted *p*-value. Selected respiratory chain-associated genes were labeled. **c,** Dot plot showing the expression of respiratory chain-associated genes across Visium clusters. Dot size represents the percentage of spots expressing each gene, and color indicates the scaled average expression. **d,** Violin plots showing the normalized expression of representative respiratory chain signature genes in each cluster. **e,** Heat map across Visium clusters 0–14; color denotes gene-wise scaled expression (z-scores). The row dendrogram shows the unsupervised hierarchical clustering of genes. Key clusters: 4, healthy leaflet tissue; 8, stenotic leaflet tissue; 10, annulus. **f–g**, Feature plots of representative respiratory chain markers. **e**, UMAP with Visium spot-level expression overlays; color indicates normalized expression (scale shown). **f,** Spatial expression maps across Visium sections encompassing the aortic valve and neighboring myocardium; color indicates normalized expression (scale shown).

Supplementary Fig.14



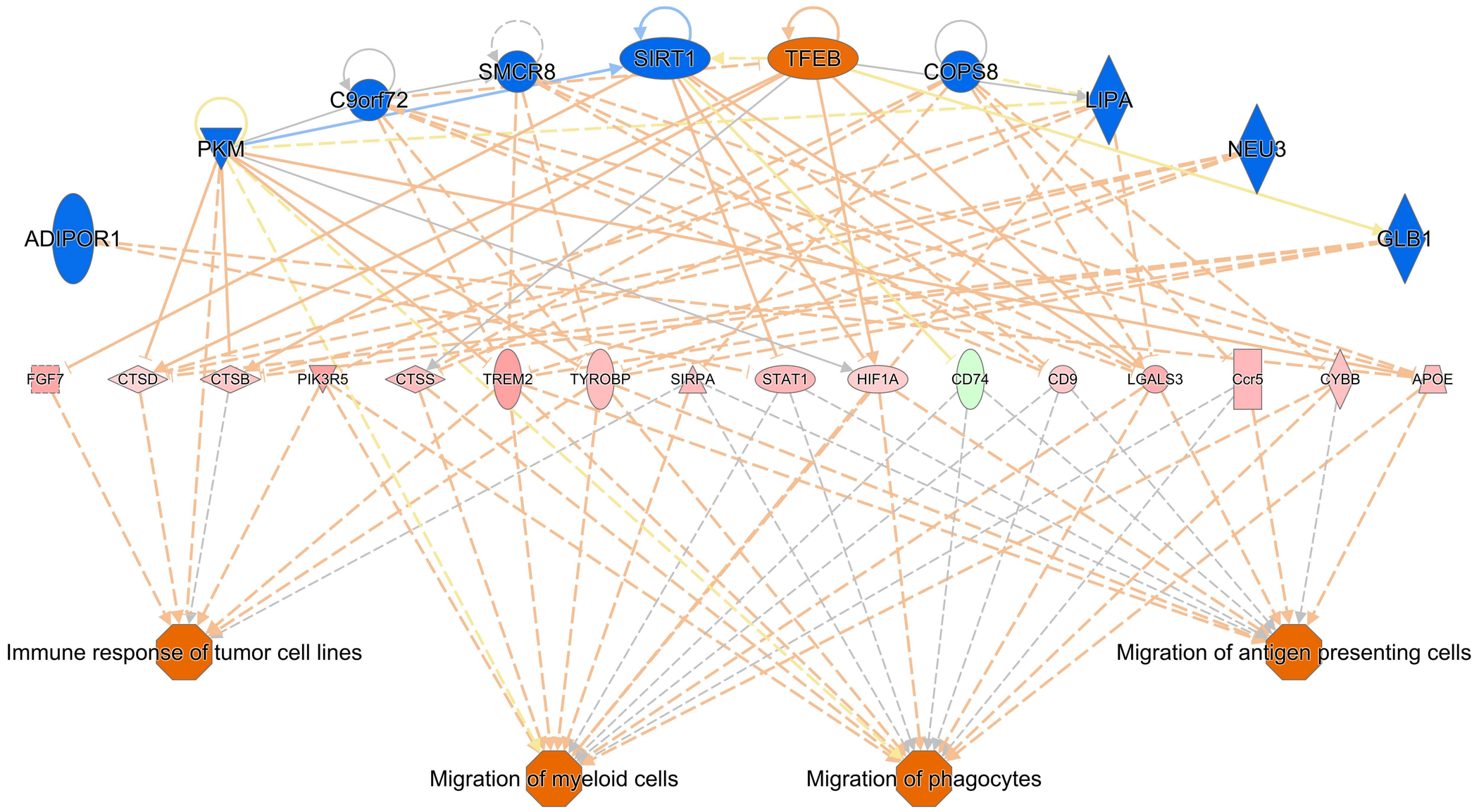
Supplementary Fig. 14 | IPA graphical summary of the effects of *Cthrc1* deficiency in early-stage AS/CAVD.
Ingenuity Pathway Analysis (IPA; QIAGEN) was performed using differentially expressed genes identified in aortic valves from *Cthrc1*$^{-/-}$ mice relative to wild-type mice during early-stage AS/CAVD. The orange and blue nodes indicate the predicted activation and inhibition, respectively, whereas the uncolored nodes have no assigned directional prediction. The orange and blue edges indicate the predicted activating and inhibitory relationships, respectively, and the grey edges indicate the relationships without directional prediction. The solid and dashed edges represent direct and indirect relationships, respectively. The graphical summary predicted activation of interferon-associated signaling and of myeloid-cell and phagocyte response programs in *Cthrc1*$^{-/-}$ mice relative to wild-type mice.

Supplementary Fig.15



Supplementary Fig. 15 | IPA canonical pathway analysis of *Cthrc1*-deficient aortic valves during early-stage AS/CAVD.
IPA was performed using DEGs identified in aortic valves from *Cthrc1*$^{-/-}$ mice relative to wild-type mice during early-stage AS/CAVD. Each bubble represents a canonical pathway and is positioned according to its functional category on the x-axis and its enrichment significance, expressed as −log10 (*p*-value of overlap), on the y-axis. Bubble size represents the number of differentially expressed genes that overlap with the pathway. Orange and blue indicate positive and negative activation z-scores, respectively; white indicates a z-score of zero; and gray indicates that no directional activity prediction was available. The selected pathways of interest were labeled. Overlap *p*-values were calculated using right-tailed Fisher's exact test. n = 3 biologically independent mice per group.

Supplementary Fig.16



Supplementary Fig. 16 | IPA regulator-effects network of *Cthrc1*-deficient aortic valves during early-stage AS/CAVD.
IPA was performed using differentially expressed genes (DEGs) identified in aortic valves from *Cthrc1*$^{-/-}$ mice relative to wild-type mice during early-stage AS/CAVD. The regulator-effects network connected predicted upstream regulators (upper layer) to the observed DEGs (middle layer) and predicted downstream biological functions (lower layer) using curated relationships in the IPA Knowledge Base. Node shapes indicate molecular or functional entity classes. Orange and blue nodes indicate predicted activation and inhibition, respectively; red and green dataset molecules indicate increased and decreased expression, respectively, in *Cthrc1*$^{-/-}$ valves relative to wild-type valves. The orange and blue edges indicate the predicted activating and inhibitory effects, respectively. The yellow edges indicate relationships inconsistent with the observed or predicted node states, and the gray edges indicate relationships without directional prediction. The solid and dashed edges represent direct and indirect relationships, respectively. This network predicted the activation of biological functions related to the migration of myeloid cells, phagocytes, and antigen-presenting cells. n = three biologically independent mice per group.

Supplementary Table 1 | Mixed-effects model analysis of AV peak velocity over time in the WI and sham groups.

Table Analyzed	WI_sham_AVpeakvel				
Mixed-effects model (REML)	Matching: Stacked				
Assume sphericity?	No				
Alpha	0.05				
Fixed effects (type III)	P value	P value summary	Statistically significant (P < 0.05)?	F (DFn, DFd)	Geisser-Greenhouse's epsilon
Time	<.001	***	Yes	F (2.627, 214.8) = 119.3	0.6567
Group	<.001	***	Yes	F (1, 169) = 393.0	
Time x Group	<.001	***	Yes	F (4, 327) = 105.3	
Random effects	SD	Variance			
Subject	218.0	47538			
Residual	380.8	144994			
Was the matching effective?					
Chi-square, df	35.84, 1				
P value	<.001				
P value summary	***				
Is there significant matching (P < 0.05)?	Yes				
Goodness of fit					
Degrees of freedom	494				
REML criterion	3731				
Difference between column means					
Predicted mean of WI	2316				
Predicted mean of Sham	1104				
Difference between predicted means	1212				
SE of difference	61.12				
95% CI of difference	1091 to 1332				
Data summary					
Number of columns (Group)	2				
Number of rows (Time)	5				
Number of subjects (Subject)	171				
Number of missing values	349				

Supplementary Table 2 | Estimated marginal means (least-squares means(LSM)) of AV peak velocity over time in the WI and sham groups.

Predicted means (LS means)	WI	Sham	Row means
baseline	1111	1075	1093
3 d	1676	1065	1371
1 wk	2557	1130	1843
2 wk	3064	1141	2102
16 wk	3173	1111	2142
Column means	2316	1104	1710

Supplementary Table 3 | Sidak-adjusted pairwise comparisons of AV peak velocity between the WI and sham groups and across time points.

Compare cell means with others in its row and its column								
Number of families	7							
Number of comparisons per row family	1							
Number of comparisons per column family	10							
Alpha	0.05							
Šídák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value			
baseline								
WI vs. Sham	37.24	-12.47 to 86.95	No	ns	0.139			
3 d								
WI vs. Sham	652.3	528.0 to 776.7	Yes	***	<.001			
1 wk								
WI vs. Sham	1459	1300 to 1618	Yes	***	<.001			
2 wk								
WI vs. Sham	1936	1803 to 2069	Yes	***	<.001			
16 wk								
WI vs. Sham	2067	1803 to 2330	Yes	***	<.001			
WI								
baseline vs. 3 d	-607.4	-725.8 to -489.0	Yes	***	<.001			
baseline vs. 1 wk	-1473	-1656 to -1291	Yes	***	<.001			
baseline vs. 2 wk	-1963	-2127 to -1799	Yes	***	<.001			
baseline vs. 16 wk	-2069	-2378 to -1759	Yes	***	<.001			
3 d vs. 1 wk	-866.1	-1022 to -710.4	Yes	***	<.001			
3 d vs. 2 wk	-1356	-1561 to -1151	Yes	***	<.001			
3 d vs. 16 wk	-1461	-1766 to -1157	Yes	***	<.001			
1 wk vs. 2 wk	-489.8	-697.9 to -281.7	Yes	***	<.001			
1 wk vs. 16 wk	-595.2	-880.8 to -309.5	Yes	***	<.001			
2 wk vs. 16 wk	-105.4	-412.0 to 201.3	No	ns	0.978			
Sham								
baseline vs. 3 d	7.711	-126.7 to 142.1	No	ns	>.999			
baseline vs. 1 wk	-51.92	-157.3 to 53.42	No	ns	0.715			
baseline vs. 2 wk	-64.83	-151.6 to 21.96	No	ns	0.275			
baseline vs. 16 wk	-39.37	-138.3 to 59.60	No	ns	0.912			
3 d vs. 1 wk	-59.63	-233.6 to 114.4	No	ns	0.949			
3 d vs. 2 wk	-72.54	-227.8 to 82.75	No	ns	0.780			
3 d vs. 16 wk	-47.08	-516.4 to 422.3	No	ns	>.999			
1 wk vs. 2 wk	-12.91	-110.6 to 84.78	No	ns	>.999			
1 wk vs. 16 wk	12.55	-9962 to 9987	No	ns	>.999			
2 wk vs. 16 wk	25.46	-51.70 to 102.6	No	ns	0.972			
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1	N2	t	DF
baseline								
WI vs. Sham	1111	1074	37.24	24.85	133	36	1.498	60.15
3 d								
WI vs. Sham	1718	1066	652.3	62.09	62	17	10.51	57.27
1 wk								
WI vs. Sham	2584	1126	1459	79.72	61	13	18.30	71.86
2 wk								
WI vs. Sham	3074	1139	1936	67.04	91	32	28.87	106.0
16 wk								
WI vs. Sham	3180	1113	2067	130.9	44	17	15.78	45.41
WI								
baseline vs. 3 d	1111	1718	-607.4	40.76	133	62	14.90	61.00
baseline vs. 1 wk	1111	2584	-1473	62.81	133	61	23.46	60.00
baseline vs. 2 wk	1111	3074	-1963	57.08	133	91	34.40	90.00
baseline vs. 16 wk	1111	3180	-2069	105.0	133	44	19.70	43.00

Supplementary Table 4 | Mixed-effects model analysis of LV mass over time in the WI and sham groups.

Table Analyzed	WI_sham_LVmass				
Mixed-effects model (REML)	Matching: Stacked				
Assume sphericity?	No				
Alpha	0.05				
Fixed effects (type III)	P value	P value summary	Statistically significant (P < 0.05)?	F (DFn, DFd)	Geisser-Greenhouse's epsilon
Time	<.001	***	Yes	F (2.628, 212.2) = 29.04	0.6569
Column Factor	0.069	ns	No	F (1, 169) = 3.351	
Time x Column Factor	0.002	**	Yes	F (4, 323) = 4.323	
Random effects	SD	Variance			
Subject	18.66	348.0			
Residual	48.34	2337			
Was the matching effective?					
Chi-square, df	10.32, 1				
P value	0.001				
P value summary	**				
Is there significant matching (P < 0.05)?	Yes				
Goodness of fit					
Degrees of freedom	490				
REML criterion	2661				
Difference between column means					
Predicted mean of WI	251.1				
Predicted mean of Sham	238.8				
Difference between predicted means	12.30				
SE of difference	6.718				
95% CI of difference	-0.9635 to 25.56				
Data summary					
Number of columns (Column Factor)	2				
Number of rows (Time)	5				
Number of subjects (Subject)	171				
Number of missing values	353				

Supplementary Table 5 | Estimated marginal means (LSM) of LV mass over time in the WI and sham groups.

Predicted means (LS means)	WI	Sham	Row means
baseline	218.5	221.7	220.1
3 d	213.8	218.7	216.3
1 wk	238.2	242.5	240.3
2 wk	248.3	236.6	242.5
16 wk	336.8	274.6	305.7
Column means	251.1	238.8	245.0

Supplementary Table 6 | Sidak-adjusted pairwise comparisons of LV mass between the WI and sham groups and across time points.

Mixed-effects analysis of WI_sham_LVmass_Multiple_comparisons

Compare cell means with others in its row and its column								
Number of families	7							
Number of comparisons per row family	1							
Number of comparisons per column family	10							
Alpha	0.05							
Šídák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value			
baseline								
WI vs. Sham	-3.380	-19.94 to 13.18	No	ns	0.684			
3 d								
WI vs. Sham	-6.221	-27.40 to 14.96	No	ns	0.552			
1 wk								
WI vs. Sham	-8.595	-49.01 to 31.82	No	ns	0.656			
2 wk								
WI vs. Sham	11.48	-13.28 to 36.25	No	ns	0.355			
16 wk								
WI vs. Sham	63.52	26.35 to 100.7	Yes	**	0.001			
WI								
baseline vs. 3 d	3.044	-12.77 to 18.86	No	ns	>.999			
baseline vs. 1 wk	-21.74	-41.87 to -1.618	Yes	*	0.026			
baseline vs. 2 wk	-30.39	-46.83 to -13.95	Yes	***	<.001			
baseline vs. 16 wk	-116.0	-154.2 to -77.85	Yes	***	<.001			
3 d vs. 1 wk	-24.79	-47.72 to -1.857	Yes	*	0.026			
3 d vs. 2 wk	-33.44	-56.15 to -10.72	Yes	***	<.001			
3 d vs. 16 wk	-119.1	-172.5 to -65.65	Yes	***	<.001			
1 wk vs. 2 wk	-8.649	-30.20 to 12.90	No	ns	0.940			
1 wk vs. 16 wk	-94.28	-151.3 to -37.24	Yes	***	<.001			
2 wk vs. 16 wk	-85.63	-120.9 to -50.40	Yes	***	<.001			
Sham								
baseline vs. 3 d	0.2033	-38.81 to 39.22	No	ns	>.999			
baseline vs. 1 wk	-26.96	-73.03 to 19.11	No	ns	0.496			
baseline vs. 2 wk	-15.53	-47.98 to 16.92	No	ns	0.824			
baseline vs. 16 wk	-49.12	-90.64 to -7.604	Yes	*	0.015			
3 d vs. 1 wk	-27.16	-84.27 to 29.94	No	ns	0.723			
3 d vs. 2 wk	-15.73	-63.62 to 32.16	No	ns	0.967			
3 d vs. 16 wk	-49.33	-188.1 to 89.42	No	ns	0.558			
1 wk vs. 2 wk	11.43	-48.34 to 71.21	No	ns	>.999			
1 wk vs. 16 wk	-22.17							
2 wk vs. 16 wk	-33.60	-78.28 to 11.08	No	ns	0.238			
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1	N2	t	DF
baseline								
WI vs. Sham	218.5	221.9	-3.380	8.244	133	36	0.4100	49.96
3 d								
WI vs. Sham	215.5	221.7	-6.221	10.32	62	17	0.6028	26.76
1 wk								
WI vs. Sham	240.3	248.9	-8.595	18.88	57	12	0.4552	14.31
2 wk								
WI vs. Sham	248.9	237.4	11.48	12.30	91	32	0.9337	45.75
16 wk								
WI vs. Sham	334.5	271.0	63.52	18.50	45	17	3.433	49.51
WI								
baseline vs. 3 d	218.5	215.5	3.044	5.444	133	62	0.5591	61.00
baseline vs. 1 wk	218.5	240.3	-21.74	6.906	133	57	3.149	56.00

Supplementary Table 7 | Mixed-effects model analysis of LV vol over time in the WI and sham groups.

Mixed-effects analysis of WI_sham_LVvol_Tabular_results

Table Analyzed	WI_sham_LVvol				
Mixed-effects model (REML)	Matching: Stacked				
Assume sphericity?	No				
Alpha	0.05				
Fixed effects (type III)	P value	P value summary	Statistically significant (P < 0.05)?	F (DFn, DFd)	Geisser-Greenhouse's epsilon
Time	<.001	***	Yes	F (2.198, 177.5) = 13.29	0.5496
Column Factor	0.040	*	Yes	F (1, 169) = 4.304	
Time x Column Factor	<.001	***	Yes	F (4, 323) = 9.516	
Random effects	SD	Variance			
Subject	4.071	16.57			
Residual	12.30	151.2			
Was the matching effective?					
Chi-square, df	5.652, 1				
P value	0.017				
P value summary	*				
Is there significant matching (P < 0.05)?	Yes				
Goodness of fit					
Degrees of freedom	490				
REML criterion	1981				
Difference between column means					
Predicted mean of WI	36.46				
Predicted mean of Sham	33.06				
Difference between predicted means	3.402				
SE of difference	1.640				
95% CI of difference	0.1647 to 6.639				
Data summary					
Number of columns (Column Factor)	2				
Number of rows (Time)	5				
Number of subjects (Subject)	171				
Number of missing values	353				

Supplementary Table 8 | Estimated marginal means (LSM) of LV vol over time in the WI and sham groups.

Predicted means (LS means)	WI	Sham	Row means
baseline	29.12	29.97	29.54
3 d	29.49	28.90	29.20
1 wk	34.41	37.01	35.71
2 wk	34.70	37.16	35.93
16 wk	54.61	32.27	43.44
Column means	36.46	33.06	34.76

Supplementary Table 9 | Sidak-adjusted pairwise comparisons of LV vol between the WI and sham groups and across time points.

Compare cell means with others in its row and its column								
Number of families	7							
Number of comparisons per row family	1							
Number of comparisons per column family	10							
Alpha	0.05							
Šídák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value			
baseline								
WI vs. Sham	-0.8730	-4.827 to 3.081	No	ns	0.659			
3 d								
WI vs. Sham	0.7193	-4.256 to 5.695	No	ns	0.769			
1 wk								
WI vs. Sham	-2.304	-11.42 to 6.809	No	ns	0.598			
2 wk								
WI vs. Sham	-2.516	-7.745 to 2.712	No	ns	0.339			
16 wk								
WI vs. Sham	22.16	12.91 to 31.40	Yes	***	<.001			
WI								
baseline vs. 3 d	-0.6716	-4.429 to 3.086	No	ns	>.999			
baseline vs. 1 wk	-5.821	-10.69 to -0.9490	Yes	**	0.010			
baseline vs. 2 wk	-5.662	-9.734 to -1.591	Yes	**	0.001			
baseline vs. 16 wk	-25.42	-35.20 to -15.63	Yes	***	<.001			
3 d vs. 1 wk	-5.149	-10.25 to -0.04355	Yes	*	0.047			
3 d vs. 2 wk	-4.991	-10.58 to 0.5964	No	ns	0.111			
3 d vs. 16 wk	-24.75	-36.53 to -12.97	Yes	***	<.001			
1 wk vs. 2 wk	0.1585	-5.447 to 5.764	No	ns	>.999			
1 wk vs. 16 wk	-19.60	-36.85 to -2.347	Yes	*	0.021			
2 wk vs. 16 wk	-19.76	-29.67 to -9.843	Yes	***	<.001			
Sham								
baseline vs. 3 d	0.9207	-9.444 to 11.29	No	ns	>.999			
baseline vs. 1 wk	-7.252	-18.40 to 3.896	No	ns	0.366			
baseline vs. 2 wk	-7.306	-14.54 to -0.06675	Yes	*	0.047			
baseline vs. 16 wk	-2.388	-12.51 to 7.730	No	ns	0.998			
3 d vs. 1 wk	-8.173	-23.93 to 7.586	No	ns	0.627			
3 d vs. 2 wk	-8.226	-20.33 to 3.872	No	ns	0.333			
3 d vs. 16 wk	-3.309	-37.27 to 30.65	No	ns	>.999			
1 wk vs. 2 wk	-0.05370	-11.40 to 11.29	No	ns	>.999			
1 wk vs. 16 wk	4.864							
2 wk vs. 16 wk	4.917	-6.566 to 16.40	No	ns	0.869			
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1	N2	t	DF
baseline								
WI vs. Sham	29.12	29.99	-0.8730	1.968	133	36	0.4435	49.83
3 d								
WI vs. Sham	29.79	29.07	0.7193	2.423	62	17	0.2968	26.60
1 wk								
WI vs. Sham	34.94	37.24	-2.304	4.271	57	12	0.5394	14.84
2 wk								
WI vs. Sham	34.78	37.30	-2.516	2.610	91	32	0.9640	56.08
16 wk								
WI vs. Sham	54.53	32.38	22.16	4.619	45	17	4.797	58.90
WI								
baseline vs. 3 d	29.12	29.79	-0.6716	1.294	133	62	0.5192	61.00
baseline vs. 1 wk	29.12	34.94	-5.821	1.672	133	57	3.482	56.00
baseline vs. 2 wk	29.12	34.78	-5.662	1.419	133	91	3.991	90.00
baseline vs. 16 wk	29.12	54.53	-25.42	3.320	133	45	7.656	44.00

Supplementary Table 10 | Mixed-effects model analysis of FS over time in the WI and sham groups.

Table Analyzed	WI_sham_FS				
Mixed-effects model (REML)	Matching: Stacked				
Assume sphericity?	No				
Alpha	0.05				
Fixed effects (type III)	P value	P value summary	Statistically significant (P < 0.05)?	F (DFn, DFd)	Geisser-Greenhouse's epsilon
Time	0.016	*	Yes	F (3.676, 301.4) = 3.216	0.9190
Group	0.015	*	Yes	F (1, 169) = 6.064	
Time x Group	0.004	**	Yes	F (4, 328) = 3.937	
Random effects	SD	Variance			
Subject	4.494	20.20			
Residual	9.764	95.33			
Was the matching effective?					
Chi-square, df	16.05, 1				
P value	<.001				
P value summary	***				
Is there significant matching (P < 0.05)?	Yes				
Goodness of fit					
Degrees of freedom	495				
REML criterion	1903				
Difference between column means					
Predicted mean of WI	59.32				
Predicted mean of Sham	62.84				
Difference between predicted means	-3.519				
SE of difference	1.429				
95% CI of difference	-6.340 to -0.6979				
Data summary					
Number of columns (Group)	2				
Number of rows (Time)	5				
Number of subjects (Subject)	171				
Number of missing values	348				

Supplementary Table 11 | Estimated marginal means (LSM) of FS over time in the WI and sham groups.

Mixed-effects analysis of WI_sham_FS_Means

Predicted means (LS means)	WI	Sham	Row means
baseline	64.90	63.20	64.05
3 d	59.34	62.88	61.11
1 wk	56.64	59.37	58.00
2 wk	60.30	61.69	61.00
16 wk	55.44	67.08	61.26
Column means	59.32	62.84	61.08

Supplementary Table 12 | Sidak-adjusted pairwise comparisons of FS between the WI and sham groups and across time points.

Compare cell means with others in its row and its column								
Number of families	7							
Number of comparisons per row family	1							
Number of comparisons per column family	10							
Alpha	0.05							
Šídák's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Below threshold?	Summary	Adjusted P Value			
baseline								
WI vs. Sham	1.656	-2.397 to 5.710	No	ns	0.416			
3 d								
WI vs. Sham	-3.886	-8.854 to 1.082	No	ns	0.121			
1 wk								
WI vs. Sham	-2.740	-8.987 to 3.506	No	ns	0.372			
2 wk								
WI vs. Sham	-1.193	-5.702 to 3.316	No	ns	0.598			
16 wk								
WI vs. Sham	-11.37	-17.82 to -4.926	Yes	***	<.001			
WI								
baseline vs. 3 d	6.434	1.994 to 10.87	Yes	***	<.001			
baseline vs. 1 wk	9.157	4.371 to 13.94	Yes	***	<.001			
baseline vs. 2 wk	4.573	0.9959 to 8.151	Yes	**	0.004			
baseline vs. 16 wk	9.319	3.169 to 15.47	Yes	***	<.001			
3 d vs. 1 wk	2.723	-2.439 to 7.885	No	ns	0.747			
3 d vs. 2 wk	-1.861	-6.730 to 3.008	No	ns	0.956			
3 d vs. 16 wk	2.885	-3.047 to 8.816	No	ns	0.764			
1 wk vs. 2 wk	-4.584	-9.049 to -0.1184	Yes	*	0.041			
1 wk vs. 16 wk	0.1617	-7.390 to 7.713	No	ns	>.999			
2 wk vs. 16 wk	4.745	-0.9368 to 10.43	No	ns	0.165			
Sham								
baseline vs. 3 d	0.8920	-6.038 to 7.822	No	ns	>.999			
baseline vs. 1 wk	4.760	-3.927 to 13.45	No	ns	0.592			
baseline vs. 2 wk	1.724	-4.849 to 8.297	No	ns	0.997			
baseline vs. 16 wk	-3.709	-11.60 to 4.178	No	ns	0.796			
3 d vs. 1 wk	3.868	-7.359 to 15.10	No	ns	0.947			
3 d vs. 2 wk	0.8319	-9.905 to 11.57	No	ns	>.999			
3 d vs. 16 wk	-4.601	-32.32 to 23.12	No	ns	0.975			
1 wk vs. 2 wk	-3.037	-12.01 to 5.939	No	ns	0.957			
1 wk vs. 16 wk	-8.470	-722.2 to 705.3	No	ns	0.991			
2 wk vs. 16 wk	-5.433	-14.43 to 3.563	No	ns	0.505			
Test details	Mean 1	Mean 2	Mean Diff.	SE of diff.	N1	N2	t	DF
baseline								
WI vs. Sham	64.90	63.24	1.656	2.017	133	36	0.8209	49.35
3 d								
WI vs. Sham	58.46	62.35	-3.886	2.436	62	17	1.595	31.05
1 wk								
WI vs. Sham	55.74	58.48	-2.740	3.000	61	13	0.9134	20.60
2 wk								
WI vs. Sham	60.32	61.52	-1.193	2.248	91	32	0.5307	53.48
16 wk								
WI vs. Sham	55.58	66.95	-11.37	3.193	45	17	3.562	41.35
WI								
baseline vs. 3 d	64.90	58.46	6.434	1.529	133	62	4.208	61.00
baseline vs. 1 wk	64.90	55.74	9.157	1.647	133	61	5.560	60.00