

SUPPLEMENTAL MATERIAL

Left Ventricular Gene Expression in Heart Failure with Preserved Ejection Fraction

Pro-fibrotic and Pro-inflammatory Pathway and Genes

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TABLE OF CONTENT

Figure S1. RNA sequencing quality.	2
Table S1. Transcriptome-based differentially regulated pathways in HFpEF.	3
Table S2. Low abundance fibrillar and nonfibrillar collagens.	4
Table S3. MMPs and TIMPs.	5
Table S4. Cytoskeletal and myofilament genes.	6

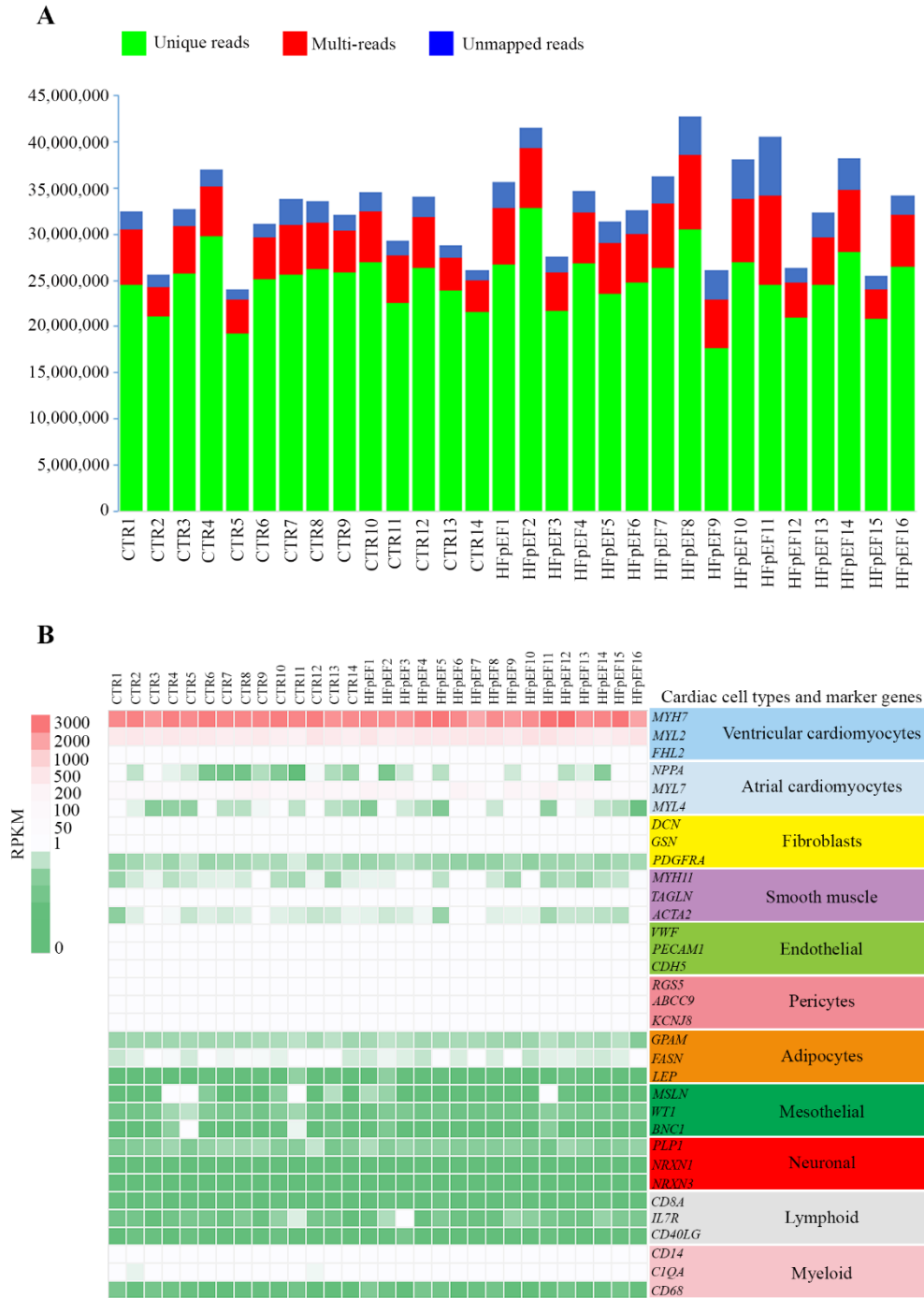


Figure S1. RNA sequencing quality. **A**, Mapping statistics of all samples for RNA sequencing. A stacked bar plot shows uniquely mapped, multiple mapped and unmapped reads against the human reference genome for each sample. **B**, Heat map detailing a representative selection of biomarker expression for the 11 major cell types among the heart biopsy samples from control (CTR) and HFpEF patients. Transcript abundances of different biomarkers were evaluated and compared in individual heart biopsy samples using reads per kilobase of transcript per million mapped reads (RPKM).

Table S1. Transcriptome-based differentially regulated pathways in HFpEF.

Name of pathway	Direction	Number of genes	Average fold change	FDR p value
Axon guidance	Down	502	-0.0524	0.0010
Nervous system development	Down	524	-0.0570	0.0010
Developmental Biology	Down	803	-0.0461	0.0020
Ligand-receptor interactions	Down	6	-0.3698	0.0030
Assembly Of The HIV Virion	Down	13	-0.0696	0.0030
APEX1-Independent Resolution of AP Sites via the Single Nucleotide Replacement Pathway	Down	7	-0.0142	0.0040
RAF activation	Up	33	0.0292	0.0040
Membrane binding and targeting of GAG proteins	Down	11	-0.0659	0.0050
Synthesis And Processing Of GAG, GAGPOL Polyproteins	Down	11	-0.0659	0.0050
DNA Damage Reversal	Up	8	0.0213	0.0060
Plasma lipoprotein clearance	Down	33	-0.0850	0.0070
Infectious disease	Up	852	0.0051	0.0070
Reversal of alkylation damage by DNA dioxygenases	Up	7	0.0433	0.0090
Formation of annular gap junctions	Down	11	-0.0284	0.0090
Gap junction degradation	Down	12	-0.0300	0.0090
LDL clearance	Down	18	-0.0770	0.0090
VLDLR internalisation and degradation	Up	13	0.0033	0.0100
RHOF GTPase cycle	Down	40	-0.0463	0.0100
VLDL clearance	Down	5	-0.3511	0.0140
CS/DS degradation	Down	13	-0.1541	0.0140
WNT5A-dependent internalization of FZD4	Up	14	0.0160	0.0150
Trafficking of AMPA receptors	Up	24	0.1625	0.0150
Glutamate binding, activation of AMPA receptors and synaptic plasticity	Up	24	0.1625	0.0150
N-glycan trimming and elongation in the cis-Golgi	Down	5	-0.1300	0.0160
Regulation of glycolysis by fructose 2,6-bisphosphate metabolism	Up	10	0.0194	0.0160
Retrograde neurotrophin signalling	Up	14	0.0744	0.0160
EPH-ephrin mediated repulsion of cells	Down	49	-0.1069	0.0160
Activation of the AP-1 family of transcription factors	Down	9	-0.2310	0.0180
SARS-CoV Infections	Up	326	0.0121	0.0190
WNT5A-dependent internalization of FZD2, FZD5 and ROR2	Up	13	0.0622	0.0230

Table S1. List of the 30 most differentially regulated pathways with at least 5 genes from the ReactomeGSA analysis based on the RNA sequencing transcriptome data. The results are ranked by p values.

Table S2. Low abundance fibrillar and nonfibrillar collagens.

Gene ID	Family	Subfamily	Mean CTR (CPM)	Mean HFpEF (CPM)	FDR p value
<i>COL2A1</i>	Fibrillar collagens		0.1698	0.1145	0.0895
<i>COL11A1</i>	Fibrillar collagens		0.2399	0.2540	0.9786
<i>COL8A2</i>	Nonfibrillar collagens	Network-forming collagens	0.7718	0.5661	0.6745
<i>COL10A1</i>	Nonfibrillar collagens	Network-forming collagens	0.1272	0.0941	0.9153
<i>COL9A1</i>	Nonfibrillar collagens	FACITs	0.5764	0.6081	0.9223
<i>COL9A2</i>	Nonfibrillar collagens	FACITs	0.7903	0.6673	0.8231
<i>COL20A1</i>	Nonfibrillar collagens	FACITs	0.0403	0.0736	0.7417
<i>COL6A5</i>	Nonfibrillar collagens	Beaded filament forming collagens	0.0000	0.0129	0.5671
<i>COL26A1</i>	Nonfibrillar collagens	Beaded filament forming collagens	0.0878	0.0511	0.7810

Table S2. List of genes encoding low abundance fibrillar and nonfibrillar collagens in control and HFpEF myocardium. The mean counts per million (CPM) values have been provided for each group, which are indicative of their respective expression levels in control and HFpEF samples. FACITs, fibril-associated collagens with interrupted triple helices.

Table S3. MMPs and TIMPs.

Gene ID	Mean CTR (CPM)	Mean HFpEF (CPM)	FDR p value
<i>MMP1</i>	0.0000	0.0544	0.5313
<i>MMP2</i>	88.7697	68.8905	0.3126
<i>MMP7</i>	0.0000	0.0092	0.5978
<i>MMP8</i>	0.0000	0.0036	0.6745
<i>MMP9</i>	0.3624	0.6330	0.5978
<i>MMP10</i>	0.0000	0.0144	0.5307
<i>MMP11</i>	4.5391	3.9548	0.7133
<i>MMP12</i>	0.0000	0.0036	0.6745
<i>MMP14</i>	14.1081	12.8899	0.8524
<i>MMP15</i>	46.5615	47.3848	0.8658
<i>MMP16</i>	5.6645	3.8409	0.3219
<i>MMP17</i>	0.9284	0.7991	0.8943
<i>MMP19</i>	1.6789	1.5386	0.9449
<i>MMP21</i>	0.3727	0.1957	0.5671
<i>MMP23A</i>	0.0601	0.0294	0.7995
<i>MMP23B</i>	0.2725	0.3976	0.6745
<i>MMP24</i>	1.6046	0.7482	0.5203
<i>MMP25</i>	0.7280	1.2631	0.5502
<i>MMP26</i>	0.0000	0.0038	0.6745
<i>MMP27</i>	0.0137	0.0000	0.5307
<i>MMP28</i>	2.8463	1.4802	0.0321
<i>TIMP1</i>	24.7221	16.3035	0.6745
<i>TIMP2</i>	84.3129	78.0020	0.7498
<i>TIMP3</i>	351.5246	268.6983	0.1814
<i>TIMP4</i>	4.9353	4.2513	0.7545

Table S3. List of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase (TIMPs) in control and HFpEF myocardium. The mean counts per million (CPM) values are provided for control and HFpEF groups.

Table S4. Cytoskeletal and myofilament genes.

Gene ID	Family	Mean CTR (CPM)	Mean HFpEF (CPM)	FDR p value
<i>DES</i>	Intermediate filament cytoskeleton	7837.8138	8501.3930	0.6464
<i>SYNM</i>	Intermediate filament cytoskeleton	777.6479	837.1178	0.6144
<i>VIM</i>	Intermediate filament cytoskeleton	186.5659	157.4826	0.5671
<i>NES</i>	Intermediate filament cytoskeleton	309.9587	378.6129	0.5307
<i>LMNA</i>	Intermediate filament cytoskeleton	128.5870	125.3578	0.9891
<i>TUBB</i>	Microtubule cytoskeleton	102.3362	96.2702	0.9352
<i>TUBB4B</i>	Microtubule cytoskeleton	114.0790	110.7394	0.9828
<i>TUBB6</i>	Microtubule cytoskeleton	36.5953	38.1524	0.7894
<i>TUBA4A</i>	Microtubule cytoskeleton	31.6231	38.4181	0.4992
<i>TUBA1A</i>	Microtubule cytoskeleton	34.3919	36.2131	0.7318
<i>ACTC1</i>	Sarcomeric actomyosin	3811.9300	3912.5995	0.7939
<i>MYH6</i>	Sarcomeric actomyosin	1650.4635	1525.9284	0.9411
<i>MYH7</i>	Sarcomeric actomyosin	60323.4541	59080.3449	0.9865
<i>ACTG1</i>	Non-sarcomeric actomyosin	161.7771	129.4963	0.4983
<i>ACTB</i>	Non-sarcomeric actomyosin	414.2081	377.1633	0.8468
<i>MYH3</i>	Non-sarcomeric actomyosin	2.4056	2.5086	0.9145
<i>MYH9</i>	Non-sarcomeric actomyosin	613.0391	604.4274	0.9490
<i>MYH11</i>	Non-sarcomeric actomyosin	92.2866	102.3031	0.6746
<i>MYH13</i>	Non-sarcomeric actomyosin	0.0314	0.0930	0.5825

Table S4. List of cytoskeletal and myofibrillar mRNAs determined by RNA sequencing in control (CTR) and HFpEF myocardium. CPM, counts per million.