

## SUPPLEMENTARY TABLES

**Supplementary Table 1. Means  $\pm$  SEM of several morphological parameters for male and female mice at 3, 12 and 24 months, Gx or not.**

<b>Males</b>	<b>3 m</b>	<b>12 m</b>	<b>24 m</b>
<b>Controls</b>			
<i>Heart, mg</i>	130 $\pm$ 4.0	167 $\pm$ 9.0	180 $\pm$ 6.5
<i>Lungs, mg</i>	128 $\pm$ 1.5	182 $\pm$ 8.2	189 $\pm$ 7.9
<i>Left atrium, mg</i>	3.6 $\pm$ 0.34	---	6.6 $\pm$ 0.41
<i>Body weight, g</i>	25.9 $\pm$ 0.62	36.7 $\pm$ 1.58	35 $\pm$ 1.6
<i>Tibial length, mm</i>	22.6 $\pm$ 0.06	22.6 $\pm$ 0.06	23.2 $\pm$ 0.15
<b>Gx</b>			
<i>Heart, mg</i>	---	139.3 $\pm$ 5.2	157 $\pm$ 4.4
<i>Lungs, mg</i>	---	158 $\pm$ 8.1	185 $\pm$ 5.9
<i>Left atrium, mg</i>	---	---	4.6 $\pm$ 0.26
<i>Body weight, g</i>	---	31.4 $\pm$ 1.95	37.6 $\pm$ 2.17
<i>Tibial length, mm</i>	---	23.4 $\pm$ 0.17	23.6 $\pm$ 0.14
<b>Females</b>	<b>3 m</b>	<b>12 m</b>	<b>24 m</b>
<b>Controls</b>			
<i>Heart, mg</i>	101 $\pm$ 2.0	122 $\pm$ 4.7	150 $\pm$ 4.6
<i>Lungs, mg</i>	118 $\pm$ 2.3	168 $\pm$ 5.9	174 $\pm$ 5.8
<i>Left atrium, mg</i>	2.8 $\pm$ 0.11	---	4.8 $\pm$ 0.43
<i>Body weight, g</i>	19.4 $\pm$ 0.29	28.5 $\pm$ 0.58	30.3 $\pm$ 1.76
<i>Tibial length, mm</i>	21.7 $\pm$ 0.10	22.1 $\pm$ 0.09	22.9 $\pm$ 0.15
<b>Gx</b>			
<i>Heart, mg</i>	---	139.3 $\pm$ 5.2	129 $\pm$ 3.4
<i>Lungs, mg</i>	---	158 $\pm$ 8.1	178 $\pm$ 5.9
<i>Left atrium, mg</i>	---	---	3.3 $\pm$ 0.21
<i>Body weight, g</i>	---	31.4 $\pm$ 1.95	31.8 $\pm$ 1.90
<i>Tibial length, mm</i>	---	23.4 $\pm$ 0.17	23.6 $\pm$ 0.14

**Supplementary Table 2. Echocardiography (Echo) data from young FCG mice at 3 months.**

<b>Parameter</b>	<b>MXV N = 13</b>	<b>FXX N = 14</b>	<b>MXX N = 15</b>	<b>FXV N = 20</b>
<b>M-Mode</b>				
EDD, mm	3,8 $\pm$ 0,05	3.7 $\pm$ 0,04	3,9 $\pm$ 0,04	3.7 $\pm$ 0,02
ESD, mm	2,7 $\pm$ 0,06	2.6 $\pm$ 0,06	2,7 $\pm$ 0,06	2.7 $\pm$ 0,05
PW, mm	0,70 $\pm$ 0,01	0.70 $\pm$ 0,01	0,75 $\pm$ 0,01*	0,69 $\pm$ 0,01
IVS, mm	0,70 $\pm$ 0,01	0,67 $\pm$ 0,01	0,72 $\pm$ 0,01	0,67 $\pm$ 0,01
RWT	0,34 $\pm$ 0,01	0,37 $\pm$ 0,01	0,38 $\pm$ 0,01*	0,37 $\pm$ 0,01
<b>Simpson's</b>				
SV, mm	31,3 $\pm$ 0,83	26.6 $\pm$ 0.66	34.2 $\pm$ 1,13	26.8 $\pm$ 0.72
EF, %	56,9 $\pm$ 1.7	57.5 $\pm$ 1.3	58.4 $\pm$ 1.4	55.8 $\pm$ 1.20
HR, bpm	444 $\pm$ 7.21	434 $\pm$ 7.8	447 $\pm$ 4.9	444 $\pm$ 5.33
CO, ml/min	13.9 $\pm$ 0,50	11.5 $\pm$ 0,32	15.3 $\pm$ 0,69	11.9 $\pm$ 0.32
EDV, $\mu$ l	55.5 $\pm$ 2,07	45.5 $\pm$ 1.13	58.6 $\pm$ 1.42	48.0 $\pm$ 0.85

ESV, $\mu$ l	24.2 $\pm$ 1.47	19.9 $\pm$ 0.92	24.5 $\pm$ 1.02	21.2 $\pm$ 0.69
<b>Doppler</b>				
E, mm/s	725 $\pm$ 25.5	663 $\pm$ 8.4	737 $\pm$ 8.53	714 $\pm$ 13.9
A, mm/s	402 $\pm$ 22.4	354 $\pm$ 12.1	461 $\pm$ 14.6	385 $\pm$ 11.5
E/A	1.85 $\pm$ 0,05	1.92 $\pm$ 0,07	1.64 $\pm$ 0,05*	1.88 $\pm$ 0,044
E', mm/s	-25.1 $\pm$ 0,99	-25.7 $\pm$ 1.07	-25.5 $\pm$ 0.56	-26.2 $\pm$ 0.71
A', mm/s	-17.9 $\pm$ 0,70	-17,6 $\pm$ 0,52	-19.2 $\pm$ 0,41	-18.8 $\pm$ 0.51
E/E'	-29.0 $\pm$ 0.98	-26.7 $\pm$ 1.19	-29.3 $\pm$ 0.75	-27.7 $\pm$ 0,76
E'/A'	1.41 $\pm$ 0,04	1.47 $\pm$ 0,04	1.34 $\pm$ 0,03	1.40 $\pm$ 0,03

Left ventricle parameters were measured in male and female mice, either XY or XX. EDD: end-diastolic LV diameter; ESD: end-systolic LV diameter; PW: diastolic posterior wall thickness; IVS: diastolic inter-ventricular septum thickness; RWT: relative wall thickness; SV: Stroke volume; EF: Ejection fraction; HR: Heart rate; CO: Cardiac output; EDV: end-diastolic volume; ESV: end-systolic volume; E: E wave; A: A wave; E': E' wave; A': A' wave. Results are expressed as the mean  $\pm$  standard error of the mean (SEM) from the indicated number of animals. Two-way ANOVA analysis and Holm-Sidak post-test. \* $p < 0.05$  vs. same sex animals.

**Supplementary Table 3. Echocardiography (Echo) data from aging non-Gx FCG mice at 20 months.**

Parameter	MX N = 11	FXX N = 11	MXX N = 13	FX N = 11
<b>M-Mode</b>				
EDD, mm	3,7 $\pm$ 0,04	3,9 $\pm$ 0,09	3,8 $\pm$ 0,06	3.8 $\pm$ 0,09
ESD, mm	2,2 $\pm$ 0,06	2,5 $\pm$ 0,11	2,4 $\pm$ 0,09	2.3 $\pm$ 0,13
PW, mm	0,81 $\pm$ 0,01	0,80 $\pm$ 0,02	0,82 $\pm$ 0,02	0,84 $\pm$ 0,01
IVS, mm	0,74 $\pm$ 0,01	0,74 $\pm$ 0,02	0,75 $\pm$ 0,01	0,75 $\pm$ 0,02
RWT	0,42 $\pm$ 0,01	0,40 $\pm$ 0,01	0,42 $\pm$ 0,01	0,42 $\pm$ 0,01
<b>Simpson's</b>				
SV, mm	32.5 $\pm$ 1.19	34.5 $\pm$ 2.20	29.8 $\pm$ 0.87	32.6 $\pm$ 1.35
EF, %	63 $\pm$ 1,2	62.2 $\pm$ 1.84	61.2 $\pm$ 1.83	63.6 $\pm$ 1.7
HR, bpm	501 $\pm$ 12.7	492 $\pm$ 22.8	515 $\pm$ 12.3	488 $\pm$ 12.4
CO, ml/min	16.3 $\pm$ 0,69	16.7 $\pm$ 1.01	15,4 $\pm$ 0,55	16.0 $\pm$ 0.93
EDV, $\mu$ l	51.3 $\pm$ 1,64	55.5 $\pm$ 3.49	49.4 $\pm$ 2,30	51.5 $\pm$ 2.4
ESV, $\mu$ l	18.9 $\pm$ 0.88	21.02 $\pm$ 1.68	19.6 $\pm$ 1.79	21.1 $\pm$ 0.59
<b>Doppler</b>				
E, mm/s	660 $\pm$ 27.7	636 $\pm$ 28.4	569 $\pm$ 21.5*	683 $\pm$ 20.9
A, mm/s	434 $\pm$ 17.6	423 $\pm$ 17.1	379 $\pm$ 9.1*	437 $\pm$ 17.0
E/A	1,52 $\pm$ 0,02	1,52 $\pm$ 0,03	1.50 $\pm$ 0,05	1.61 $\pm$ 0,04
E', mm/s	-31.1 $\pm$ 1.33	-31.4 $\pm$ 0.99	-29.8 $\pm$ 0,59	-32.0 $\pm$ 0.59
A', mm/s	-20.4 $\pm$ 1.19	-20.6 $\pm$ 0.47	-18.7 $\pm$ 0.59	-19.8 $\pm$ 0.83
E/E'	-21.7 $\pm$ 1.46	-20.0 $\pm$ 0.83	-19.2 $\pm$ 0.78	-21.4 $\pm$ 0.59
E'/A'	1.54 $\pm$ 0.02	1.52 $\pm$ 0,03	1.6 $\pm$ 0,04	1.59 $\pm$ 0,04

Left ventricle parameters were measured in male and female mice, either XY or XX. Abbreviations: EDD: end-diastolic LV diameter; ESD: end-systolic LV diameter; PW: diastolic posterior wall thickness; IVS: diastolic inter-ventricular septum thickness; RWT: relative wall thickness; SV: Stroke volume; EF: Ejection fraction; HR: Heart rate; CO: Cardiac output; EDV: end-diastolic volume; ESV: end-systolic volume; E: E wave; A: A wave; E': E' wave; A': A' wave. Results are expressed as the mean  $\pm$  standard error of the mean (SEM) from the indicated number of animals. Two-way ANOVA analysis and Holm-Sidak post-test. \* $p < 0.05$  vs. same sex animals.

**Supplementary Table 4. Echocardiography (Echo) data from young gonadectomized FCG mice at 3 months.**

Parameter	MX N = 8	FX N = 8	MX N = 6	FX N = 8
<b>M-Mode</b>				
EDD, mm	3,7 ± 0,05	3,7 ± 0,04	3,9 ± 0,02	3,9 ± 0,02
ESD, mm	2,7 ± 0,08	2,5 ± 0,07	2,8 ± 0,07	2,8 ± 0,07
PW, mm	0,69 ± 0,02	0,74 ± 0,02	0,65 ± 0,02	0,65 ± 0,02**
IVS, mm	0,71 ± 0,02	0,72 ± 0,01	0,63 ± 0,02*	0,63 ± 0,01**
RWT	0,38 ± 0,01	0,39 ± 0,01	0,33 ± 0,01*	0,33 ± 0,01*
<b>Simpson's</b>				
SV, mm	29.1 ± 1.42	33.0 ± 0.67	34.2 ± 1.24	29,0 ± 1.14
EF, %	57.8 ± 2,43	66.2 ± 1,21	57.8 ± 2.62	54,7 ± 1,94*
HR, bpm	451 ± 13.0	480 ± 11.4	468 ± 18.3	407 ± 16,2*
CO, ml/min	13.2 ± 0.85	15.8 ± 0,41	15.0 ± 0.33	11.9 ± 0.88
EDV, µl	50.7 ± 2,01	49.9 ± 0.64	57.8 ± 2.61	53,0 ± 1.09
ESV, µl	21.6 ± 1.79	16.9 ± 0.66	25.5 ± 1.45	24.0 ± 1.15*
<b>Doppler</b>				
E, mm/s	694 ± 26.8	673 ± 17.1	711 ± 23.6	676 ± 21.7
A, mm/s	432 ± 20.4	437 ± 17.6	443 ± 8.41	376 ± 14.0*
E/A	1.63 ± 0,07	1.56 ± 0,04	1.60 ± 0,03	1.82 ± 0.07*
E', mm/s	-24.5 ± 1.43	-26.8 ± 1.65	-25.4 ± 0.97	-24.6 ± 1.35
A', mm/s	-17.5 ± 0.90	-17,7 ± 0,59	-18.1 ± 0.86	-19.5 ± 0.97
E/E'	-29.4 ± 1.99	-25.9 ± 1.36	-28.9 ± 1.53	-27.9 ± 0,78
E'/A'	1,42 ± 0,08	1,51 ± 0,08	1,42 ± 0,08	1,26 ± 0,01**

Left ventricle parameters were measured in male and female mice, either XY or XX. Abbreviations: EDD: end-diastolic LV diameter; ESD: end-systolic LV diameter; PW: diastolic posterior wall thickness; IVS: diastolic inter-ventricular septum thickness; RWT: relative wall thickness; SV: Stroke volume; EF: Ejection fraction; HR: Heart rate; CO: Cardiac output; EDV: end-diastolic volume; ESV: end-systolic volume; E: E wave; A: A wave; E': E' wave; A': A' wave. Results are expressed as the mean ± standard error of the mean (SEM) from the indicated number of animals. Two-way ANOVA analysis and Holm-Sidak post-test. \* $p < 0.05$  and \*\* $p < 0.01$  vs. same sex animals.

**Supplementary Table 5. Echocardiography (Echo) data from aging gonadectomized FCG mice at 20 months.**

Parameter	MX N = 7	FX N = 5	MX N = 7	FX N = 7
<b>M-Mode</b>				
EDD, mm	3,7 ± 0,04	3,9 ± 0,10	3,8 ± 0,08	3,7 ± 0,09
ESD, mm	2,1 ± 0,07	2,3 ± 0,15	2,3 ± 0,10	2,0 ± 0,04
PW, mm	0,79 ± 0,02	0,86 ± 0,04	0,82 ± 0,02	0,84 ± 0,03
IVS, mm	0,70 ± 0,01	0,78 ± 0,03	0,76 ± 0,03	0,75 ± 0,02
RWT	0,40 ± 0,01	0,43 ± 0,02	0,42 ± 0,01	0,43 ± 0,01
<b>Simpson's</b>				
SV, mm	32.4 ± 1.41	35.5 ± 1.82	32.5 ± 1.69	32.9 ± 1.42
EF, %	65.4 ± 1.12	64.2 ± 2.44	64.2 ± 0.97	67.6 ± 1.0
HR, bpm	487 ± 16.3	508 ± 12.8	494 ± 7.2	497 ± 8.3
CO, ml/min	15.8 ± 0.84	18.0 ± 0.78	16.0 ± 0.89	16.3 ± 0.53
EDV, µl	49.5 ± 1.85	55.5 ± 3.59	50.6 ± 2.65	48.8 ± 2.2

ESV, $\mu$ l	17.1 $\pm$ 0.81	20.0 $\pm$ 2.49	18.1 $\pm$ 1.13	15.9 $\pm$ 1.01
<b>Doppler</b>				
E, mm/s	607 $\pm$ 22.5	663 $\pm$ 26.5	632 $\pm$ 29.3	636 $\pm$ 31.2
A, mm/s	363 $\pm$ 9.6	390 $\pm$ 9.6	409 $\pm$ 10.9*	395 $\pm$ 14.0
E/A	1.70 $\pm$ 0.04	1.70 $\pm$ 0.06	1.55 $\pm$ 0.06	1.61 $\pm$ 0.03
E', mm/s	-29.6 $\pm$ 0.38	-29.6 $\pm$ 0.56	-30.8 $\pm$ 1.44	-28.5 $\pm$ 0.63
A', mm/s	-16.7 $\pm$ 0.39	-17.4 $\pm$ 1.15	-18.5 $\pm$ 1.26	-17.6 $\pm$ 0.70
E/E'	-20.5 $\pm$ 0.78	-22.4 $\pm$ 1.09	-20.6 $\pm$ 0.85	-22.3 $\pm$ 0.92
E'/A'	1.80 $\pm$ 0.04	1.74 $\pm$ 0.11	1.68 $\pm$ 0.06	1.63 $\pm$ 0.06

Left ventricle parameters were measured in male and female mice, either XY or XX. Abbreviations: EDD: end-diastolic LV diameter; ESD: end-systolic LV diameter; PW: diastolic posterior wall thickness; IVS: diastolic inter-ventricular septum thickness; RWT: relative wall thickness; SV: Stroke volume; EF: Ejection fraction; HR: Heart rate; CO: Cardiac output; EDV: end-diastolic volume; ESV: end-systolic volume; E: E wave; A: A wave; E': E' wave; A': A' wave. Results are expressed as the mean  $\pm$  standard error of the mean (SEM) from the indicated number of animals. Two-way ANOVA analysis and Holm-Sidak post-test. \* $p < 0.05$  vs. same-sex animals.

#### Supplementary Table 6. Differentially regulated LV genes between 24-month-old males and 24-month-old females.

<b>Lower expression in females</b>			
Gene	Mean count	log <sub>2</sub> (FC)	q-Value
<b>Ddx3y</b>	<b>775.2</b>	<b>-7.25</b>	<b>2.53E-04</b>
<b>Eif2s3y</b>	<b>526.89</b>	<b>-6.62</b>	<b>9.05E-04</b>
<b>Uty</b>	<b>227.66</b>	<b>-6.54</b>	<b>2.60E-05</b>
<b>Kdm5d</b>	<b>216.57</b>	<b>-6.23</b>	<b>0.00E+00</b>
Cyp26b1	953.58	-3.17	2.60E-05
C7	357.49	-2.45	0.00E+00
Ppbp	60.56	-2.24	1.46E-03
Itga2b	70.33	-1.79	2.10E-02
Atp2b2	51.79	-1.37	3.21E-03
Npas2	85.14	-1.3	3.08E-02
Kcnk1	113.37	-1.28	1.80E-04
Prom2	91.29	-1.18	8.38E-04
Tmem171	59.41	-1.17	4.95E-02
Aqp8	143.92	-1.1	3.52E-03
<b>Higher expression in females</b>			
<b>Xist</b>	<b>3969.72</b>	<b>9.24</b>	<b>0.00E+00</b>
Car3	52.27	2.64	7.00E-06
Lypd8l	129.99	1.47	6.12E-04
Col14a1	634.85	1.41	0.00E+00
Ptn	91.13	1.07	2.78E-02
Erdr1	1099.73	1.06	1.00E-06
Dkk3	229.81	1.06	7.85E-03
Kcne1	74.77	1.06	1.40E-02
Lepr	151.48	1.01	1.60E-03

Mean count: Normalized mean count (male vs. female), FC: fold change and q-value: the proportion of false positives among all positive results. In bold, sex chromosome genes.

**Supplementary Table 7. Differentially regulated LV genes between 24-month-old males and 24-month-old Gx males.**

<b>Lower expression in Gx males</b>			
<b>Gene</b>	<b>Mean Count</b>	<b>log<sub>2</sub>(FC)</b>	<b>q-Value</b>
C7	364.22	-1.96	1.00E-06
Lcn2	60.24	-1.94	5.00E-06
Cnmd	70.31	-1.43	6.98E-03
Klk1b26	51.86	-1.32	3.66E-02
Cyp2b10	209.23	-1.28	2.26E-04
Mmp3	183.84	-1.04	6.38E-03
<b>Higher expression in Gx males</b>			
Lrrc55	56.78	2.15	0.00E+00
Col14a1	635.06	1.49	0.00E+00
Ptn	94.82	1.24	6.98E-03
Mdk	60.65	1.1	9.50E-03

Mean count: Normalized mean count (male vs. female), FC: fold change and *q*-value: the proportion of false positives among all positive results.

**Supplementary Table 8. Differentially regulated LV genes between 24-month-old females and 24-month-old Gx females.**

<b>Lower expression in Gx females</b>			
<b>Gene</b>	<b>Mean count</b>	<b>log<sub>2</sub>(FC)</b>	<b>q-Value</b>
Fkbp5	672.41	-1.1	2.30E-05
Ifi205	379.99	-1.02	3.60E-05
Zbtb16	3608.46	-1	7.86E-03

Mean count: Normalized mean count (male vs. female), FC: fold change and *q*-value: the proportion of false positives among all positive results.