Dual linkage of a locus to left ventricular mass and a cardiac gene co-expression network driven by a chromosome domain
Supplemental Table S1: Characteristics of 8 c3-QTL genes on chromosome 13

| gene name       | start position | gene exp LOD | correlation with LVM | drop Lvm1 LOD | residual Lvm1 LOD |
|-----------------|----------------|--------------|----------------------|---------------|------------------|
| Golm1           | 59.73          | 5.9          | 0.73                 | 3.59          | 1.01             |
| 4930486i24rik   | 60.94          | 7.4          | 0.58                 | 2.21          | 2.39             |
| Hapb4           | 64.26          | 5.9          | 0.70                 | 3.47          | 1.13             |
| Cdk20/ccrk      | 64.53          | 10.8         | -0.68                | 3.11          | 1.49             |
| Cdc14b          | 64.29          | 7.7          | 0.68                 | 3.00          | 1.60             |
| Ctsl            | 64.46          | 13.6         | 0.66                 | 2.94          | 1.66             |
| Zfp367          | 64.24          | 8.9          | -0.63                | 2.67          | 1.93             |
| Aaed1           | 64.39          | 14.5         | 0.60                 | 2.34          | 2.26             |

The start positions refer to the transcription start sites of corresponding genes on chromosome 13 (in Mb). The “drop Lvm1 LOD” corresponds to the decrease in value of the LOD score of Lvm1 after using the expression level of each corresponding gene as a covariate for QTL mapping. The “residual Lvm1 LOD” corresponds to the LOD score of Lvm1 obtained after using the expression level of each corresponding gene as a covariate for QTL mapping.
### Supplemental Table S2: Characteristics of module QTLs (mQTLs) of “genetic” modules

| Type of module | Module Names       | main mQTL position | mQTL LOD | matching cis-eQTL clusters |
|----------------|--------------------|---------------------|----------|---------------------------|
| CDD            | bisque4            | 15@76.4             | 12.64    | 15@76.6                   |
| CDD            | brown4             | 9@44.5              | 11.67    | 9@44.2 / 9@44.8           |
| CDD            | darkolivegreen     | 11@98.8             | 10.15    | 11@96.8                   |
| CDD            | darkred            | 6@144.9             | 6.43     | 6@145.1                   |
| CDD            | darkturquoise      | 9@105.9             | 17.9     | 9@106                     |
| CDD            | lightcyan1         | 13@113.2            | 9.9      | 13@113.7                  |
| CDD            | midnightblue       | 4@133.4             | 11.7     | 4@113.9                   |
| CDD            | orangered4         | 17@33.1             | 16.76    | 17@34                     |
| CDD            | palevioletred3     | 4@154.5             | 9.32     | 4@155.2                   |
| CDD            | plum1              | 2@26.1              | 6.83     | 2@25.2                    |
| CDD            | royalblue          | 11@57               | 7.35     | 11@58                     |
| CDD            | skyblue3           | 1@172.9             | 16       | 1@172.9                   |
| CDD            | thistle2           | 13@64.8             | 12.2     | 13@64.3                   |
| CDD            | cyan               | 2@113.4             | 14.1     | 2@103.9                   |
| CDD            | floralwhite        | 7@105.8             | 11.8     | ~                         |
| CDD            | ivory              | 12@110.3            | 11.7     | ~                         |
| CDD            | lightsteelblue1    | 13@47               | 6.8      | ~                         |
| CDD            | mediumpurple3      | 7@50.6              | 9.3      | ~                         |
| CDD            | plum2              | 17@9.08             | 16       | ~                         |
| CDD            | sienna3            | 14@46.2             | 13.53    | ~                         |
| CDD            | thistle1           | 5@119.3             | 10.35    | ~                         |
| non-CDD        | darkslateblue      | 1@94.8              | 4.13     |                           |
| non-CDD        | orange             | 1@116.9             | 3.9      |                           |
| non-CDD        | pink               | 17@84.1             | 3.85     |                           |
| non-CDD        | saddlebrown        | 17@89.2             | 4.1      |                           |
| non-CDD        | salmon             | 12@101.7            | 5.8      |                           |
| non-CDD        | skyblue            | 16@20.4             | 4.16     |                           |

The modules showing linkage to one main mQTL were divided into those showing evidence (or not) of being “chromosome-domain driven” (CDD). The names of each module correspond to those given by the WGCNA program. The characteristics of each mQTL correspond to the number of the chromosome harboring the mQTL, followed by its position (in Mb) on the chromosome. For 16/21 CDD modules, the peak of their mQTL was in very close vicinity of the position of a “cis-eQTL cluster”, as reported by us previously (doi:10.1534/g3.112.005488).
### Supplemental Table S3: Properties of genes from “genetic” modules

| Type of module | Module Names | % of cis-eQTLs among module genes | % of module genes from predom. chrom. | Predom. Chrom. # | mean Interval between genes from pred. chr. (Mb) | relative connectivity of genes from predom. chrom. vs. others |
|----------------|--------------|-----------------------------------|--------------------------------------|-----------------|-----------------------------------------------|--------------------------------------------------|
| CDD            | bisque4      | 22.41%                            | 50.00%                               | 15              | 8.13                                          | 2.56                                             |
| CDD            | brown4       | 42.37%                            | 54.24%                               | 9               | 11.02                                         | 2.87                                             |
| CDD            | darkolivegreen | 32.38%                           | 56.19%                               | 11              | 13.34                                         | 2.38                                             |
| CDD            | darkred      | 15.17%                            | 27.59%                               | 6               | 16.13                                         | 2.14                                             |
| CDD            | darkturquoise | 24.65%                            | 42.25%                               | 9               | 16.50                                         | 3.53                                             |
| CDD            | lightcyan1   | 14.08%                            | 22.54%                               | 13              | 14.25                                         | 4.34                                             |
| CDD            | midnightblue | 40.12%                            | 30.23%                               | 8               | 22.58                                         | 1.57                                             |
| CDD            | orangered4   | 16.46%                            | 58.23%                               | 17              | 12.67                                         | 3.94                                             |
| CDD            | palevioletred3 | 27.91%                           | 34.88%                               | 4               | 11.89                                         | 2.95                                             |
| CDD            | plum1        | 26.25%                            | 51.25%                               | 2               | 50.13                                         | 3.58                                             |
| CDD            | royalblue    | 17.01%                            | 26.53%                               | 11              | 19.21                                         | 2.53                                             |
| CDD            | skyblue3     | 31.87%                            | 41.76%                               | 1               | 19.26                                         | 5.18                                             |
| CDD            | thistle2     | 32.65%                            | 30.61%                               | 13              | 13.13                                         | 3.23                                             |
| CDD            | cyan         | 15.61%                            | 39.31%                               | 2               | 38.05                                         | 3.25                                             |
| CDD            | floralwhite  | 22.39%                            | 41.79%                               | 7               | 21.66                                         | 3.95                                             |
| CDD            | ivory        | 10.29%                            | 32.35%                               | 12              | 5.55                                          | 2.81                                             |
| CDD            | lightsteelblue1 | 36.11%                        | 36.11%                               | 13              | 18.03                                         | 2.59                                             |
| CDD            | mediumpurple3 | 29.11%                            | 56.96%                               | 7               | 29.18                                         | 2.96                                             |
| CDD            | plum2        | 27.27%                            | 56.36%                               | 17              | 19.31                                         | 2.68                                             |
| CDD            | sienna3      | 3.13%                             | 30.21%                               | 14              | 8.61                                          | 5.17                                             |
| CDD            | thistle1     | 22.92%                            | 47.92%                               | 5               | 15.99                                         | 2.11                                             |
| mean           |              |                                   |                                      |                 |                                               |                                                  |
| SD             |              |                                    |                                      |                 |                                               |                                                  |
| CDD            |              | 24.29%                            | 41.30%                               |                 | 18.3                                          | 3.2                                              |
| genetic non-CDD|              | 6.09%                             | 12.28%                               |                 | 51.5                                          | 1.0                                              |
| mean           |              |                                    |                                      |                 |                                               |                                                  |
| genetic non-CDD|              | 9.97%                             | 11.48%                               |                 | 10.3                                          | 0.9                                              |
| SD             |              |                                    |                                      |                 |                                               |                                                  |
| genetic non-CDD|              | 3.97%                             | 2.08%                                |                 | 12.1                                          | 0.1                                              |
### Supplemental Table S4: Properties of genes from “non-genetic” modules

| Type of module   | Module Names | % of cis-eQTLs among module genes | % of module genes from predom. chrom. | Predom. Chrom. # | mean Interval between genes from pred. chr. (Mb) | relative connectivity of genes from predom. chrom. vs. others |
|------------------|--------------|-----------------------------------|---------------------------------------|------------------|-----------------------------------------------|---------------------------------------------------------------|
| non-genetic      | black        | 2.29%                             | 11.11%                                | 11               | 32.14                                         | 1.04                                                          |
| non-genetic      | blue         | 1.60%                             | 8.68%                                 | 11               | 41.88                                         | 0.77                                                          |
| non-genetic      | brown        | 4.09%                             | 8.64%                                 | 2                | 52.58                                         | 1.15                                                          |
| non-genetic      | darkgreen    | 6.29%                             | 9.79%                                 | 2                | 62.61                                         | 1.15                                                          |
| non-genetic      | darkgrey     | 4.93%                             | 14.08%                                | 10               | 54.85                                         | 1.04                                                          |
| non-genetic      | darkmagenta  | 3.49%                             | 8.33%                                 | 11               | 35.08                                         | 0.86                                                          |
| non-genetic      | darkorange   | 3.67%                             | 9.29%                                 | 10               | 43.45                                         | 0.91                                                          |
| non-genetic      | darkorange2  | 0.00%                             | 8.96%                                 | 14               | 24.44                                         | 0.85                                                          |
| non-genetic      | green        | 3.37%                             | 10.67%                                | 7                | 62.93                                         | 1.01                                                          |
| non-genetic      | greenyellow  | 2.67%                             | 10.67%                                | 3                | 44.76                                         | 0.99                                                          |
| non-genetic      | grey60       | 1.86%                             | 9.32%                                 | 9                | 35.42                                         | 1.12                                                          |
| non-genetic      | lightcyan    | 1.54%                             | 12.62%                                | 11               | 40.86                                         | 0.90                                                          |
| non-genetic      | lightyellow  | 6.49%                             | 14.29%                                | 2                | 62.59                                         | 0.81                                                          |
| non-genetic      | paleturquoise| 0.00%                             | 11.32%                                | 5                | 57.00                                         | 0.91                                                          |
| non-genetic      | salmon4      | 2.17%                             | 13.04%                                | 11               | 19.50                                         | 0.89                                                          |
| non-genetic      | steelblue    | 3.48%                             | 13.04%                                | 5                | 49.19                                         | 0.80                                                          |
| non-genetic      | tan          | 1.64%                             | 14.21%                                | 10               | 30.12                                         | 0.96                                                          |
| non-genetic      | turquoise    | 3.82%                             | 8.79%                                 | 9                | 45.22                                         | 0.73                                                          |
| non-genetic      | violet       | 0.94%                             | 10.38%                                | 5                | 58.83                                         | 0.81                                                          |
| non-genetic      | white        | 2.48%                             | 8.26%                                 | 19               | 6.27                                          | 1.02                                                          |
| non-genetic      | yellow       | 2.42%                             | 10.48%                                | 3                | 52.77                                         | 1.13                                                          |
| non-genetic      | yellowgreen  | 1.09%                             | 11.96%                                | 1                | 82.19                                         | 1.04                                                          |
| mean             |              | 2.74%                             | 10.81%                                |                  | 45.2                                          | 1.0                                                           |
| SD               |              | 1.74%                             | 2.01%                                 |                  | 17.0                                          | 0.1                                                           |
Supplemental Table S5: Additional information concerning the eight c3-QTL genes on chromosome 13

| gene symbol | Gene name                                                | A vs B allele cardiac expression | Potential function in heart | Gene ontology annotation                        |
|-------------|----------------------------------------------------------|----------------------------------|-----------------------------|------------------------------------------------|
| Golm1       | golgi membrane protein 1                                 | ↑ 32%                            | None reported               | nucleus organization                             |
| 4930486l24rik | Testin-2                                               | ↑ 19%                            | None reported               | cysteine-type peptidase activity                 |
| Hap4        | hyaluronic acid binding protein 4                        | ↓ 63%                            | None reported               | hyaluronic acid binding                          |
| Cdk20/ccrk  | cyclin-dependent kinase 20                               | ↑ 13%                            | Promotes LVH                | cyclin-dependent protein kinase activity         |
| Cdc14b      | cell division cycle 14B                                  | ↑ 35%                            | None reported               | phosphoprotein phosphatase activity / DNA repair |
| Ctsl        | cathepsin L                                             | ↑ 51%                            | Protects against LVH        | cysteine-type peptidase activity                 |
| Zfp367      | zinc finger protein 367                                 | ↑ 54%                            | None reported               | regulation of transcription, DNA-templated       |
| Aaed1       | AhpC/TSA antioxidant enzyme domain containing 1          | ↑ 18%                            | None reported               | Not determined                                  |

For Cdk20 and Ctsl, information concerning their potential roles in the heart is as indicated in the discussion of the manuscript.
Supplemental Figure S1: QTL mapping profiles for LVM and 9 cis-eQTL genes from chr13 whose expression correlates significantly with LVM. **Fig. S1a:** genome-wide profiles; **Fig. 1b:** profiles at the level of chr13. For LVM, the horizontal black and grey lines correspond to the threshold levels of significant and suggestive QTLs, respectively. The light grey vertical lines represent the confidence interval for the phenotypic QTL \( Lvm1 \). The darker vertical lines correspond to the confidence intervals for the QTL of each respective gene. The confidence intervals of the first 8 cis-eQTLs fell within the boundaries of the confidence interval for \( Lvm1 \); the confidence interval of the eQTL for Fastkd3 fell just outside of these boundaries.

Supplemental Figure S2: QTL mapping profiles of the 8 c3-QTL genes on chr 13, either before (black lines) or after (gray lines) using LVM as a covariate for QTL mapping. In each case, residual variance is still such that each cis-eQTL peak remains clearly detectable.

Supplemental Figure S3: Effects of varying parameters on the prediction strength of the network (in comparison to the network constructed with the default parameters). Effects are shown for varying: 1) the soft thresholding \( \beta \) variable (**upper left**); 2) the deepSplit variable of the cutreeDynamic function (**upper right**); 3) the minClusterSize of the cutreeDynamic function (**lower left**); and 4) the cutHeight values of the mergeCloseModules function (**lower right**). The vertical lines correspond to the prediction strength found for the network with default values (corresponding to a value = 1). Prediction strength was maintained to high values over a wide range of variations of the last three values.

Supplemental Figure S4: Effects of variations of the soft thresholding \( \beta \) variable on the membership of most connected gene within detected modules. The black and grey lines corresponded to the top 20% and 40% most connected genes, respectively.

Supplemental Figure S5: QTL mapping profiles (at the level of chr13) for LVM, for the thistle2 module, and 5 trans-eQTLs. The peak of the mQTL and that of all 5 trans-eQTLs fell within the boundaries of the confidence interval for \( Lvm1 \).
Supplemental Figure S6: Diagram representation and properties of the plum2 the co-expression module. The size of each node is proportional to the connectivity of each corresponding gene; the width of each edge is proportional to the strength of correlation between the two corresponding genes. Each node is color-coded in the following fashion: the red nodes comprised a physical cluster of 22 eQTL genes all contained within a 6 Mb interval on chr 17 (from positions 21 to 26.5 Mb); the pink nodes represent other genes on chr17; the grey nodes represent all other module genes. The linear regression shows that each module gene correlates with LVM in a fashion that is directly proportional to their connectivity index (defined as the log2 transformation of the connectivity value calculated by WGCNA) ($r^2 = 0.37$, $P < 0.0001$). The pie chart shows that as much as 34 (out of a total of 51) module genes physically originated from chr 17. The bar graphs (mean ± SD) show that the connectivity of module genes and their correlation with LVM is proportional to their classification in the three respective groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).
Supplemental Fig. S1a
Supplemental Fig. S1b
Supplemental Fig. S3

- **Soft Thresholding**
  - X-axis: prediction strength value
  - Y-axis: soft thresholding

- **Deep Split**
  - X-axis: deep split
  - Y-axis: prediction strength value

- **Min Cluster Size**
  - X-axis: min cluster size
  - Y-axis: prediction strength value

- **Cut Height**
  - X-axis: cut height
  - Y-axis: prediction strength value
Supplemental Fig. S4

Graph showing two line plots: one for top 20% and another for top 40%. The x-axis represents soft thresholding, and the y-axis shows percentage. The graph illustrates the percentage distribution across different soft thresholding values.
Supplemental Fig. S6