**Supplemental Table 1:** Genomic inflation values (λ) for analyses of left ventricular traits in HyperGEN (N = 1,934).

|  |  |  |  |
| --- | --- | --- | --- |
| **Left ventricular traits** | **Single-variant analysis** | **MAF < 1%** | **MAF < 5%** |
| **Burden** | **MB** | **SKAT** | **VT** | **Burden** | **MB** | **SKAT** | **VT** |
| **LVM** | 1 | 0.99 | 0.97 | 1 | 0.98 | 1 | 0.99 | 1.1 | 0.99 |
| **LVIDD** | 1 | 0.97 | 0.98 | 0.99 | 0.94 | 0.99 | 0.98 | 1 | 0.94 |
| **RWT** | 1 | 1 | 1 | 0.97 | 0.94 | 1 | 1 | 1 | 0.97 |
| **FS** | 1 | 0.96 | 0.94 | 0.91 | 0.82 | 1 | 0.94 | 0.97 | 0.85 |
| **E/A ratio** | 1 | 0.97 | 0.97 | 0.98 | 0.9 | 0.95 | 0.95 | 0.99 | 0.89 |
| **LAD** | 1 | 0.97 | 0.95 | 0.98 | 0.94 | 0.97 | 0.98 | 1 | 0.95 |

LVM: Left Ventricular Mass; LVIDD: Left Ventricular Internal Dimension-Diastole; RWT: Relative Wall Thickness; FS: Fractional Shortening; E/A ratio: The ratio of left ventricular transmitral early velocity to late/atrial velocity; LAD: Left Atrial Dimension. LVM, LVIDD, RWT, and E/A ratio were natural log-transformed. LAD was square-rooted. MB: The Madsen-Browning weighted burden test; SKAT: The Sequence Kernel Association Test; VT: The Variable Frequency Threshold Test.

**Supplemental Table 2:** The top variants from the single-variant analysis with minor allele frequency ≥ 0.5% in HyperGEN (N = 1,934) with false discovery rate correction.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Left ventricular traits** | **SNP** | **Chr** | **Position** | **Gene** | **SNP function** | **MAF** | **Beta** | **FDR**  |
| **LAD** | rs45470697 | 5 | 149212624 | *PPARGC1B* | R330W | 0.06 | -0.04 | 0.004 |
| **LAD** | rs45519432 | 5 | 149212802 | *PPARGC1B* | S389Y | 0.06 | -0.04 | 0.004 |
| **E/A ratio** | rs8176919 | 16 | 3706697 | *DNASE1* | G127R | 0.06 | 0.08 | 0.02 |
| **FS** | rs11555566 | 20 | 43255220 | *ADA* | K80R | 0.07 | 1.54 | 0.022 |
| **FS** | rs36009281 | 5 | 70798541 | *BDP1* | K722E | 0.01 | -3.58 | 0.024 |
| **E/A ratio** | rs41277210 | 1 | 216144049 | *USH2A* | R2292H | 0.01 | 0.23 | 0.033 |
| **FS** | rs138346219 | 3 | 46307313 | *CCR3* | I243V | 0.27 | -5.16 | 0.043 |

The models were adjusted for age, gender, center, body mass index and first 10 principal components. LAD: Left Atrial Dimension;

E/A ratio: The ratio of left ventricular transmitral early velocity to late/atrial velocity; LVIDD: Left Ventricular Internal Dimension-

Diastole; RWT: Relative Wall Thickness; FS: Fractional Shortening; LAD was square-rooted. E/A ratio, LVIDD, and RWT were

natural log-transformed. MAF: Minor Allele Frequency; FDR: False Discovery Rate.

**Supplemental Table 3:** The top results from gene-based analysis across traits in HyperGEN N = 1,934 (the smallest p-value for each gene is shown in bold) with false discovery rate correction.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Left ventricular traits** | **Gene****name** | **Gene-based association p-values** | **MAF cumulative (Total # of carriers)** | **Top single-variant signal** |
| **MAF < 1%** | **MAF < 5%** | **SNP** | **MAF** | **FDR** |
| **Burden** | **MB** | **SKAT** | **VT** | **Burden** | **MB** | **SKAT** | **VT** |  |  |  |
| **E/A ratio** | *KCNH4* | **0.001**(++) | **0.001**(++) | 0.06(++) | **0.001**(++) | **0.001**(++) | **0.001**(++) | 0.06(++) | **0.001**(++) | 1.6\*10-3(6) | rs139161684 | 8.1\*10-4 | 1.7\*10-5 |
| **LAD** | *ENDOG* | 0.99(++) | **0.002**(++) | 0.99(++) | N/A | 0.99(++) | **0.002**(++) | 0.99(++) | N/A | 2.4\*10-3(9) | rs186499200 | 2.6\*10-4 | 1.9\*10-6 |
| **LVIDD** | *RAMP1* | 0.47(+++) | **0.004**(+++) | 0.99(+++) | 0.03(++) | 0.47(+++) | **0.004**(+++) | 0.99(+++) | 0.03(++) | 4.2\*10-3(16) | rs142335491 | 5.3\*10-4 | 0.99 |

\*The models were adjusted for age, gender, center, body mass index and first 10 principal components. Direction of SNPs contributing gene-based analysis inside parentheses. Plus means

increase, minus means decrease compared to common alleles (additive model). E/A ratio: The ratio of left ventricular transmitral early velocity to late/atrial velocity; LAD: Left Atrial Dimension;

LVIDD: Left Ventricular Internal Dimension-Diastole. E/A ratio and LVIDD were natural log-transformed. LAD was square-rooted. MB: the Madsen-Browning weighted burden test; SKAT: the

Sequence Kernel Association Test. VT: the Variable Frequency Threshold Test; MAF: Minor Allele Frequency; MAF cumulative and total number of carriers for the most significant test. FDR:

False Discovery Rate.

**Supplemental Table 4:** The top results from gene-based analysis across five traits in HyperGEN N = 1,934 from sensitivity analysis (the smallest p-value for each gene is shown in bold).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Left ventricular traits | Genename | Gene-based association p-values | MAF cumulative (Total # of carriers) | Top single-variant signal |
| MAF < 1% | MAF < 5% | SNP | MAF | p-value |
| Burden | MB | SKAT | VT | Burden | MB | SKAT | VT |
| E/A ratio | KCNH4 | 1.2\*10-10(++) | 1.2\*10-10(++) | 5.1\*10-6(++) | 1.2\*10-10(++) | 1.2\*10-10(++) | 1.2\*10-10(++) | 5.1\*10-6(++) | 1.2\*10-10(++) | 1.6\*10-3(6) | rs139161684 | 8.1\*10-4 | 2.0\*10-10 |
| LAD | ENDOG | 0.003(++) | 1.0\*10-7(++) | 0.009(++) | N/A | 0.003(++) | 1.0\*10-7(++) | 0.009(++) | N/A | 2.4\*10-3(9) | rs186499200 | 2.6\*10-4 | 2.2\*10-11 |
| LVIDD | RAMP1 | 7.1\*10-5(+++) | 5.5\*10-7(+++) | 0.006(+++) | 1.7\*10-6(++) | 7.1\*10-5(+++) | 5.5\*10-7(+++) | 0.006(+++) | 1.5\*10-6(++) | 4.2\*10-3(16) | rs142335491 | 5.3\*10-4 | 4.6\*10-5 |
| E/A ratio | PHKB | 6.6\*10-5(+++++++++-) | 1.3\*10-5(+++++++++-) | 0.005(+++++++++-) | NA | 1.8\*10-4(++++++++++-) | 6.0\*10-6(++++++++++-) | 0.02(++++++++++-) | NA | 0.04(142) | rs117218785 | 5.4\*10-4 | 5.8\*10-5 |
| LAD | GPR55 | NA | NA | NA | NA | 0.16(++) | 4.1\*10-5(++) | 0.07(++) | NA | 0.02(93) | rs141404889 | 7.9\*10-4 | 2.1\*10-7 |

\*The model was adjusted for age, gender, center, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, using anti-hypertensive medication (Yes/No), and first 10

principal components. Direction of SNPs contributing gene-based analysis inside parentheses. Plus means increase, minus means decrease compared to common alleles (additive model). E/A

ratio: The ratio of left ventricular transmitral early velocity to late/atrial velocity; LAD: Left Atrial Dimension; LVIDD: Left Ventricular Internal Dimension-diastole. E/A ratio and LVIDD were natural

log-transformed. LAD was square-rooted. MB: The Madsen-Browning Weighted Burden Test; SKAT: The Sequence Kernel Association Test; VT: The Variable Frequency Threshold Test; MAF:

Minor Allele Frequency. MAF cumulative and total number of carriers for the most significant test.

**Supplemental Table 5:** The top results from gene-based analysis of E/A ratio from subjects with transmitral annulus velocities fully recoded (N = 1,221) in HyperGEN (the smallest p-value for each gene is shown in bold).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Left ventricular traits** | **Gene****name**  | **Gene-based association p-values** | **MAF cumulative (Total # of carriers)** | **Top single-variant signal** |
| **MAF < 1%** | **MAF < 5%** | **SNP**  | **MAF**  | **p-value**  |
| **Burden** | **MB** | **SKAT** | **VT** | **Burden** | **MB** | **SKAT** | **VT** |
| **E/A ratio** | *KCNH4* | **2.8\*10-6** | **2.8\*10-6** | 6.2\*10-6 | **2.8\*10-6** | **2.8\*10-6** | **2.8\*10-6** | 6.2\*10-6 | **2.8\*10-6** | 2.5\*10-3 | rs139161684 | 1.2\*10-3 | 2.2\*10-8 |
| (++) | (++) | (++) | (++) | (++) | (++) | (++) | (++) | -6 |
| **E/A ratio** | *PHKB* | 4.4\*10-4 | 7.8\*10-5 | 0.004 | 4.4\*10-4 | 8.1\*10-4 | **4.2\*10-5** | 0.02 | 4.8\*10-4 | 0.04 | rs117218785 | 8.2\*10-4 | 7.4\*10-5 |
| (+++++++---) | (+++++++---) | (+++++++---) | (++++++--) | (++++++++---) | (++++++++---) | (++++++++---) | (++++++--) | -102 |

\*The models were adjusted for age, gender, center, body mass index and first 10 principal components. Direction of SNPs contributing gene-based analysis inside parentheses. Plus means

increase, minus means decrease compared to common alleles (additive model). E/A ratio: The ratio of left ventricular transmitral early velocity to late/atrial velocity. E/A ratio was natural logtransformed.

MB: The Madsen-Browning Weighted Burden Test; SKAT: The Sequence Kernel Association Test; VT: The Variable Frequency Threshold Test; MAF: Minor Allele Frequency.

MAF cumulative and total number of carriers for the most significant test.