**Supplemental Table 1:** list of the 24 SNPs included in the *NPPB* – *NPPA* gene candidate analysis

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Rs name | chr | pos | A1 | A2 | N0 | N1 | N2 | NAs | callrate | maf | hz |
| rs2272803 | 1 | 11898789 | T | G | 3 | 130 | 1442 | 0 | 1.000 | 0.043 | 0.083 |
| rs1023252\* | 1 | 11899033 | T | G | 128 | 603 | 844 | 0 | 1.000 | 0.273 | 0.383 |
| rs198415 | 1 | 11901592 | C | T | 23 | 348 | 1201 | 3 | 0.998 | 0.125 | 0.221 |
| rs61764042 | 1 | 11905059 | G | A | 3 | 76 | 1496 | 0 | 1.000 | 0.026 | 0.048 |
| rs5065 | 1 | 11906068 | G | A | 27 | 364 | 1184 | 0 | 1.000 | 0.133 | 0.231 |
| rs198370 | 1 | 11906981 | C | T | 8 | 234 | 1327 | 6 | 0.996 | 0.080 | 0.149 |
| rs61757261 | 1 | 11907430 | G | T | 0 | 4 | 1571 | 0 | 1.000 | 0.001 | 0.003 |
| rs5063 | 1 | 11907648 | T | C | 4 | 141 | 1430 | 0 | 1.000 | 0.047 | 0.090 |
| rs198372 | 1 | 11909514 | A | G | 20 | 358 | 1197 | 0 | 1.000 | 0.126 | 0.227 |
| rs149772863 | 1 | 11917720 | A | G | 0 | 5 | 1570 | 0 | 1.000 | 0.002 | 0.003 |
| rs35640285 | 1 | 11918379 | A | C | 0 | 8 | 1567 | 0 | 1.000 | 0.003 | 0.005 |
| rs5229 | 1 | 11918519 | T | C | 0 | 13 | 1562 | 0 | 1.000 | 0.004 | 0.008 |
| rs198389\* | 1 | 11919271 | G | A | 295 | 786 | 493 | 1 | 0.999 | 0.437 | 0.499 |
| rs79712000 | 1 | 11924030 | C | T | 2 | 112 | 1461 | 0 | 1.000 | 0.037 | 0.071 |
| rs6676300\* | 1 | 11925300 | G | A | 224 | 751 | 599 | 1 | 0.999 | 0.381 | 0.477 |
| rs4846061 | 1 | 11926350 | A | C | 4 | 165 | 1405 | 1 | 0.999 | 0.055 | 0.105 |
| rs74714707 | 1 | 11926758 | T | C | 2 | 111 | 1462 | 0 | 1.000 | 0.037 | 0.070 |
| rs12562952 | 1 | 11927056 | C | T | 11 | 288 | 1276 | 0 | 1.000 | 0.098 | 0.183 |
| rs9661078 | 1 | 11936324 | C | A | 209 | 805 | 559 | 2 | 0.999 | 0.389 | 0.512 |
| rs11804222 | 1 | 11936514 | A | G | 14 | 320 | 1240 | 1 | 0.999 | 0.111 | 0.203 |
| rs79593079 | 1 | 11936644 | T | C | 2 | 129 | 1444 | 0 | 1.000 | 0.042 | 0.082 |
| rs7554327 | 1 | 11937404 | T | C | 375 | 829 | 371 | 0 | 1.000 | 0.499 | 0.526 |
| rs4846066 | 1 | 11938050 | A | G | 208 | 803 | 560 | 4 | 0.997 | 0.388 | 0.511 |
| rs72864766 | 1 | 11938399 | A | G | 4 | 145 | 1426 | 0 | 1.000 | 0.049 | 0.092 |

SNP, single nucleotide polymorphism; Chr, chromosome; pos, position; A1, allele 1; A2, allele 2; N0, number of homozygotes for A1; N1, number of heterozygotes; N2, number of homozygotes for A2, NAs, number of missing data; MAF, minor allele frequency; hz, heterozygosity, \* these SNPs were also identified in the GWAS.

**Supplemental Table 2 :** **Characteristics of the subjects not included in the study (n=150)**

|  |  |
| --- | --- |
| **Characteristics** | **Mean ± sd / n (%)** |
| Age (years) | 49.77 ± 13.54 |
| Sex female  | 78 (52.00%) |
| Current smoker | 38 (25.50%) |
| BMI (kg/m²) | 26.85 ± 5.41 |
| Diabetes | 2 (1.40%) |
| Fasting glycemia (g/L) | 0.88 ± 0.11 |
| Glycated hemoglobin (%) | 5.57 ± 0.36 |
| eGFR (mL/min/1.73m²) | 96.38 ± 13.44 |
| Urinary sodium (mmol/L) | 109.31 ± 43.59 |
| Heart Rate (bpm) | 62.70 ± 9.91 |
| SBP (mmHg) | 121.04 ± 11.03 |
| DBP (mmHg) | 74.66 ± 8.27 |
| Hypertension | 62 (41.33%) |
| Any CV conditions\* | 4 (2.67%) |
| Heart failure | 1 (0.67%) |
| Myocardial infarction | 0 (0.00%) |
| Stroke | 2 (1.33%) |
| Valvular disease | 2 (1.33%) |
| Septal e’ (cm/s) | 9.61 ± 2.79 |
| Lateral e’ (cm/s) | 12.74 ± 4.11 |
| e/a | 1.19 ± 0.44 |
| e/e' | 6.55 ±1.65 |
| LAVI (mL) | 23.34 ± 7.68 |
| Deceleration time | 204.31 ± 53.56 |
| NT-proBNP levels according to category of subjects (arbitrary PEA units) |  |
|  Healthy (n=87) | 3.54 ± 1.00 |
|  Hypertension (n=59) | 3.74 ± 1.08 |
|  Any CV conditions\* (n=4) | 4.11 ± 1.07 |

\*Any CV conditions included Heart failure, Myocardial infarction, Stroke and Valvular diseases.

**Supplemental Table 3:** Covariate effects in the linear model for plasma NT-proBNP levels

|  |  |  |
| --- | --- | --- |
|  | Univariate model | Multivariate model |
|   | Estimate | SD | P value | Estimate | SD | P value |
| Sex (female) | 0.536 | 0.044 | <0.001 | 0.026  | 0.002  | <0.001 |
| Age | 0.028 | 0.002 | <0.001 | 0.556  | 0.0504 | <0.001 |
| BMI | -0.011 | 0.008 | 0.025 | -0.006  | 0.005  | 0.224  |
| eGFR | -0.006 | 0.002 | 0.003 | -0.006  | 0.002  | 0.003  |
| HR | -0.016 | 0.002 | <0.001 | -0.015  | 0.002  | <0.001 |
| SBP | -0.005 | 0.002 | 0.056 | -0.003  | 0.002  | 0.220  |
| Urinary Na | 0.00087 | 0.00050 | 0.08 | 0.0015 | 0.0005 | 0.005  |

SD, standard deviation; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; SBP, Systolic Blood Pressure; Urinary Na, urinary sodium

**Supplemental Table 4**: Variance decomposition for plasma NT-proBNP levels for all included subjects

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Heritability | Common environmental effect | Covariate effects | Residual variance |
| Model 1 | 16.31 | 1.64 | 19.83 | 62.20 |
| Model 2 | 15.11 | 0.65 | 22.97 | 61.27 |

Model 1, covariates are age and sex; Model 2, covariates are age, sex, eGFR, heart rate and urinary sodium

**Supplemental Table 5**: Variance decomposition for plasma NT-proBNP levels among healthy subjects

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Heritability | Common environmental effect | Covariate effects | Residual variance |
| Model 1 | 16.23 | 0.00 | 20.66 | 63.10 |
| Model 2 | 15.95 | 0.00 | 23.31 | 60.73 |

Model 1, covariates are age and sex; Model 2, covariates are age, sex, eGFR, heart rate and urinary sodium

**Supplemental table 6**: Correlations between the gene expressions of the gene cluster.

|  |  |  |
| --- | --- | --- |
|  |  | Correlation Coefficient |
|  |  | NPPB | NPPA | MTHFR | CLCN6 | C1orf167 |
| P value | NPPB |  | 0.049 | -0.016 | 5.10-4 | 0.090 |
| NPPA | 0.25 |  | -0.030 | -0.062 | **0.167** |
| MTHFR | 0.71 | 0.49 |  | 0.073 | -0.026 |
| CLCN6 | 0.99 | 0.14 | 0.08 |  | 0.065 |
| C1orf167 | 0.06 | **<0.001** | 0.54 | 0.13 |  |



**Supplemental Figure 1: Comparison between measured by clinical routine assays and the PEA technology**