**Supplementary Material: Gut microbiome and atrial fibrillation – results from a large population-based study**

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**Supplementary Table 1.** Characteristics of the study sample compared to individuals excluded due to missing covariates.

|  |  | **Missing covariate** |  |
| --- | --- | --- | --- |
|  | **Study sample** | **Alcohol consumption** | **Register data** | **Current smoker** | **Other** | **p** |
| N  | 6763 | 286 | 115 | 30 | 17 |  |
| Age, years (SD) | 49.19 (12.88) | 55.31 (13.03) | 48.41 (12.93) | 60.54 (11.07) | 53.45 (16.07) | <0.001 |
| Women, N (%) | 3680 (54.4) | 196 (68.5) | 70 (60.9) | 17 (56.7) | 9 (52.9) | <0.001 |
| Body mass index, kg/m² (SD) | 26.95 (4.63) | 28.02 (5.13) | 26.80 (5.07) | 27.87 (5.19) | 31.97 (9.74) | <0.001 |
| Systolic blood pressure, mm Hg (SD) | 135.63 (20.23) | 138.74 (20.25) | 134.90 (23.60) | 143.77 (20.84) | 150.69 (25.33) | 0.001 |
| Diabetes mellitus, N (%) |  |  |  |  |  | <0.001 |
| 0 | 6392 (94.5) | 257 (89.9) | 0 (0.0) | 27 (90.0) | 15 (88.2) |  |
| 1 | 371 (5.5) | 29 (10.1) | 0 (0.0) | 3 (10.0) | 2 (11.8) |  |
| NA  | 0 (0.0) | 0 (0.0) | 115 (100.0) | 0 (0.0) | 0 (0.0) |  |
| Current smoker, N (%) |  |  |  |  |  | <0.001 |
| 0 | 5169 (76.4) | 229 (80.1) | 87 (75.7) | 0 (0.0) | 14 (82.4) |  |
| 1 | 1594 (23.6) | 52 (18.2) | 28 (24.3) | 0 (0.0) | 3 (17.6) |  |
| NA  | 0 (0.0) | 5 (1.7) | 0 (0.0) | 30 (100.0) | 0 (0.0) |  |
| Antihypertensive medication, N (%) |  |  |  |  |  | <0.001 |
| 0 | 5547 (82.0) | 214 (74.8) | 0 (0.0) | 18 (60.0) | 11 (64.7) |  |
| 1 | 1216 (18.0) | 72 (25.2) | 0 (0.0) | 12 (40.0) | 6 (35.3) |  |
| NA  | 0 (0.0) | 0 (0.0) | 115 (100.0) | 0 (0.0) | 0 (0.0) |  |
| Total cholesterol, mmol/l (SD) | 5.59 (1.06) | 5.77 (1.04) | 5.64 (1.27) | 5.58 (0.96) | 5.29 (1.59) | 0.089 |
| Alcohol consumption, g (SD) | 80.40 (121.96) | NaN (NA) | 75.03 (93.28) | 41.84 (71.14) | 73.68 (104.38) | 0.032 |
| Prevalent atrial fibrillation, N (%) |  |  |  |  |  | <0.001 |
| 0 | 6647 (98.3) | 281 (98.3) | 0 (0.0) | 30 (100.0) | 14 (82.4) |  |
| 1 | 116 (1.7) | 5 (1.7) | 0 (0.0) | 0 (0.0) | 3 (17.6) |  |
| NA  | 0 (0.0) | 0 (0.0) | 115 (100.0) | 0 (0.0) | 0 (0.0) |  |
| Incident atrial fibrillation, N (%) |  |  |  |  |  | <0.001 |
| 0 | 6224 (92.0) | 259 (90.6) | 0 (0.0) | 27 (90.0) | 15 (88.2) |  |
| 1 | 539 (8.0) | 27 (9.4) | 0 (0.0) | 3 (10.0) | 2 (11.8) |  |
| NA  | 0 (0.0) | 0 (0.0) | 115 (100.0) | 0 (0.0) | 0 (0.0) |  |
| Heart failure, N (%) |  |  |  |  |  | <0.001 |
| 0 | 6669 (98.6) | 281 (98.3) | 0 (0.0) | 27 (90.0) | 15 (88.2) |  |
| 1 | 94 (1.4) | 5 (1.7) | 0 (0.0) | 3 (10.0) | 2 (11.8) |  |
| NA  | 0 (0.0) | 0 (0.0) | 115 (100.0) | 0 (0.0) | 0 (0.0) |  |

Statistical model performed to test group differences is χ2 test for categorical variables and one-way analysis of variance for continuous variables.

**Supplementary Table 2.** Common microbial genera (N=91, prevalence ≥1%, abundance ≥0.1%).

| **Ace–Dia** | **Die–Lac** | **Mar–Vei** |
| --- | --- | --- |
| Acetivibrio | Dielma | Marvinbryantia |
| Acidaminococcus | Dorea | Megamonas |
| Actinomyces | Eggerthella | Megasphaera |
| Adlercreutzia | Eisenbergiella | Methanobrevibacter |
| Akkermansia | Enorma | Methanomassiliicoccus |
| Alistipes | Enterobacter | Mitsuokella |
| Alloprevotella | Enterococcus | Odoribacter |
| Anaerostipes | Erysipelatoclostridium | Oscillibacter |
| Anaerotruncus | Escherichia | Parabacteroides |
| Bacteroides | Escherichia\* | Paraprevotella |
| Bacteroides\* | Eubacterium | Parasutterella |
| Barnesiella | Eubacterium\* | Phascolarctobacterium |
| Bifidobacterium | Faecalibacterium | Phocea |
| Bilophila | Faecalicatena | Porphyromonas |
| Bittarella | Faecalicoccus | Prevotella |
| Blautia | Faecalitalea | Roseburia |
| Butyricicoccus | Fournierella | Ruminiclostridium |
| Butyricimonas | Gordonibacter | Ruminococcus |
| Butyrivibrio | Haemophilus | Ruthenibacterium |
| Catenibacterium | Halapricum | Sanguibacteroides |
| Caudovirales | Holdemanella | Sellimonas |
| Cellulomonas | Holdemania | Senegalimassilia |
| Citrobacter | Hungatella | Shigella |
| Clostridioides | Intestinibacter | Solobacterium |
| Clostridium | Johnsonella | Streptococcus |
| Collinsella | Klebsiella | Subdoligranulum |
| Coprobacillus | Klebsiella\* | Sutterella |
| Coprobacter | Kluyvera | Tannerella |
| Coprococcus | Lachnoanaerobaculum | Turicibacter |
| Dakarella | Lachnoclostridium | Tyzzerella |
| Desulfovibrio | Lactobacillus | Veillonella |
| Dialister | Lactococcus |  |

Bacterial plasmids are denoted with an asterisk.

**Supplementary Table 3.** Baseline characteristics of the validation case-control study.

|  |  |  |
| --- | --- | --- |
| **Variable** | **No prevalent AF (N=** **74)** | **Prevalent AF (N=64)** |
| Age, years (SD) | 61.8 (8.8) | 58.8 (11.0) |
| Women, N (%) | 25 (33.8) | 15 (23.4) |
| Body mass index, kg/m² (SD) | 24.4 (2.7) | 26.3 (3.2) |
| Systolic blood pressure, mmHg (SD) | 124 (14) | 127 (18) |
| Diabetes mellitus, N (%) | 2 (2.7) | 1 (1.6) |
| Current smoker, N (%) | 12 (16.2) | 4 (6.2) |
| Antihypertensive medication, N (%) | 9 (12.2) | 36 (56.2) |
| Alcohol consumption, N (%) | 63 (85.1) | 48 (75.0) |
| Heart failure, N (%) | 0 (0.0) | 3 (4.7) |

Data are provided as mean (standard deviation [SD]) number (%).

**Supplementary Table 4.** Replication of top genera from FINRISK in the validation cohort.

| **Bacterium** | **Log2-fold change (FINRISK)** | **Cliff’s Delta (AF vs vs CTRL, LONE-AF)** | **Significant under** |
| --- | --- | --- | --- |
| *Enorma* | 0.91 | 0.04 | Prevalent AF |
| *Holdemanella* | -0.80 | 0.06 | Prevalent AF |
| *Eisenbergiella* | 0.81 | -0.06 | Prevalent AF |
| *Kluyvera* | 1.07 | 0.02 | Prevalent AF |
| *Parabacteroides* | -0.47 | -0.09 | Prevalent AF |
| *Turicibacter* | -0.74 | 0.06 | Prevalent AF |
| *Enterobacter* | 0.88 | NA | Prevalent AF |
| *Bacteroides* | -0.79 | -0.16 | Prevalent AF |
| *Bifidobacterium* | -0.49 | -0.01 | Prevalent AF |
| *Desulfovibrio* | 0.56 | -0.05 | Prevalent AF |
| **Bacterium** | **Log2-fold change (FINRISK)** | **Cliff’s Delta (AF vs vs CTRL, LONE-AF)** | **Significant under** |
| *Sellimonas* | 1.02 | NA | Incident AF – DESeq2 |
| *Mitsuokella* | 1.02 | 0.07 | Incident AF – DESeq2 |
| *Enorma* | 0.46 | 0.04 | Incident AF – DESeq2 |
| *Tyzzerella* | -0.32 | 0.01 | Incident AF – DESeq2 |
| *Bifidobacterium* | 0.37 | -0.01 | Incident AF – DESeq2 |
| *Lactococcus* | 0.47 | 0.10 | Incident AF – DESeq2 |
| *Hungatella* | -0.20 | -0.04 | Incident AF – DESeq2 |
| *Sanguibacteroides* | -0.26 | NA | Incident AF – DESeq2 |
| *Lactobacillus* | 0.27 | 0.05 | Incident AF – DESeq2 |
| *Eisenbergiella* | -0.24 | -0.06 | Incident AF – DESeq2 |
| **Bacterium** | **Cox estimate (FINRISK)** | **Cliff’s Delta (AF vs vs CTRL, LONE-AF)** | **Significant under** |
| *Odoribacter* | -0.09 | -0.08 | Incident AF – Cox regression |
| *Solobacterium* | 0.09 | NA | Incident AF – Cox regression |
| *Sanguibacteroides* | -0.06 | NA | Incident AF – Cox regression |
| *Collinsella* | 0.04 | 0.27 | Incident AF – Cox regression |
| *Enorma* | 0.07 | 0.04 | Incident AF – Cox regression |
| *Barnesiella* | -0.04 | -0.28 | Incident AF – Cox regression |
| *Paraprevotella* | -0.04 | -0.01 | Incident AF – Cox regression |
| *Alistipes* | -0.06 | -0.03 | Incident AF – Cox regression |
| *Enterococcus* | -0.06 | 0.05 | Incident AF – Cox regression |
| *Clostridium* | 0.08 | -0.07 | Incident AF – Cox regression |

The table shows the bacterial genera from main Table 2-4 together with their effect size in comparison between AF cases and controls in the validation cohort. Provided are Cliff's Delta nonparametric effect size estimates. AF stands for atrial fibrillation.

**Supplementary Table 5.** Sensitivity analysis for incident AF by limiting follow-up to 7.5 years or by including extra covariates (physical activity and diet).

|  | **Log2 Fold change ± Standard error** | **FDR-corrected P value** | **Significance** |
| --- | --- | --- | --- |
| **Feature** | **7.5 y followup** | **Extra covariates** | **7.5 y followup** | **Extra covariates** | **7.5 y followup** | **Extra covariates** |
| Acetivibrio | +0.04 ± +0.03 | -0.02 ± +0.03 | 0.5811723 | 0.8317909 |  |  |
| Acidaminococcus | -0.02 ± +0.16 | +0.19 ± +0.14 | 0.9977793 | 0.5058338 |  |  |
| Actinomyces | -0.03 ± +0.06 | -0.06 ± +0.05 | 0.936578 | 0.6613658 |  |  |
| Adlercreutzia | +0.11 ± +0.09 | +0.06 ± +0.08 | 0.541924 | 0.8317909 |  |  |
| Akkermansia | -0.18 ± +0.15 | -0.21 ± +0.66 | 0.5991643 | 0.9986098 |  |  |
| Alistipes | -0.10 ± +0.07 | -0.11 ± +0.06 | 0.5047783 | 0.2732354 |  |  |
| Alloprevotella  | -0.13 ± +0.07 | -0.13 ± +0.06 | 0.2852478 | 0.1525482 |  |  |
| Anaerostipes  | +0.05 ± +0.07 | +0.01 ± +0.06 | 0.8775415 | 0.9986098 |  |  |
| Anaerotruncus | -0.09 ± +0.04 | +0.00 ± +0.04 | 0.2512203 | 0.9986098 |  |  |
| Bacteroides | -0.13 ± +0.07 | -0.13 ± +0.06 | 0.2737719 | 0.1525482 |  |  |
| Bacteroides\*  | -0.12 ± +0.15 | -0.09 ± +0.13 | 0.8046785 | 0.8696827 |  |  |
| Barnesiella | -0.01 ± +0.11 | -0.02 ± +0.10 | 0.9977793 | 0.9986098 |  |  |
| **Bifidobacterium** | -0.05 ± +0.09 | +0.34 ± +0.08 | 0.9086224 | 0.0004373 |  | \*\*\* |
| Bilophila | -0.11 ± +0.13 | -0.06 ± +0.11 | 0.8046785 | 0.9417014 |  |  |
| Bittarella  | -0.04 ± +0.03 | -0.02 ± +0.03 | 0.6758472 | 0.9360358 |  |  |
| Blautia | -0.08 ± +0.05 | -0.04 ± +0.04 | 0.451381 | 0.8091458 |  |  |
| Butyricicoccus  | -0.05 ± +0.04 | -0.00 ± +0.03 | 0.4871292 | 0.9986098 |  |  |
| Butyricimonas | -0.10 ± +0.10 | -0.00 ± +0.09 | 0.7407844 | 0.9986098 |  |  |
| Butyrivibrio  | +0.19 ± +0.13 | +0.03 ± +0.11 | 0.451381 | 0.9986098 |  |  |
| Catenibacterium | -0.30 ± +0.15 | +0.07 ± +0.13 | 0.2512203 | 0.9360358 |  |  |
| Caudovirales  | -0.20 ± +0.44 | -0.01 ± +0.38 | 0.936578 | 0.9986098 |  |  |
| Cellulomonas  | +0.09 ± +0.13 | +0.09 ± +0.12 | 0.8676294 | 0.8317909 |  |  |
| Citrobacter | -0.02 ± +0.53 | +0.12 ± +0.50 | 0.9977793 | 0.9986098 |  |  |
| Clostridioides  | +0.10 ± +0.07 | +0.06 ± +0.06 | 0.451381 | 0.6746623 |  |  |
| Clostridium | -0.00 ± +0.05 | +0.04 ± +0.04 | 0.9977793 | 0.8317909 |  |  |
| Collinsella | -0.04 ± +0.09 | +0.11 ± +0.08 | 0.936578 | 0.5058338 |  |  |
| Coprobacillus | -0.09 ± +0.07 | -0.02 ± +0.06 | 0.5824871 | 0.9986098 |  |  |
| Coprobacter | -0.13 ± +0.08 | -0.15 ± +0.07 | 0.4148807 | 0.1525482 |  |  |
| Coprococcus | +0.04 ± +0.06 | +0.01 ± +0.05 | 0.8775415 | 0.9986098 |  |  |
| Dakarella | -0.10 ± +0.95 | -0.11 ± +0.83 | 0.9977793 | 0.9986098 |  |  |
| Desulfovibrio | -0.03 ± +0.11 | +0.06 ± +0.10 | 0.9977793 | 0.9041222 |  |  |
| Dialister | -0.07 ± +0.15 | +0.25 ± +0.13 | 0.936578 | 0.192958 |  |  |
| Dielma  | -0.42 ± +0.13 | -0.32 ± +0.12 | 0.0194592 | 0.043436 | \* | \* |
| Dorea | -0.05 ± +0.06 | -0.11 ± +0.05 | 0.8046785 | 0.1525482 |  |  |
| Eggerthella | +0.08 ± +0.10 | +0.01 ± +0.09 | 0.8046785 | 0.9986098 |  |  |
| **Eisenbergiella**  | -0.90 ± +0.11 | -0.53 ± +0.09 | 0 | 0.0000002 | \*\*\* | \*\*\* |
| **Enorma**  | -0.16 ± +0.08 | +0.30 ± +0.07 | 0.2659044 | 0.0004243 |  | \*\*\* |
| Enterobacter  | +0.33 ± +0.16 | +0.29 ± +0.14 | 0.2272609 | 0.1525482 |  |  |
| Enterococcus  | -0.05 ± +0.32 | -0.08 ± +0.29 | 0.9977793 | 0.9986098 |  |  |
| Erysipelatoclostridium  | +0.00 ± +0.08 | +0.06 ± +0.07 | 0.9977793 | 0.8091458 |  |  |
| Escherichia | -0.12 ± +1.08 | +0.04 ± +0.97 | 0.9977793 | 0.9986098 |  |  |
| Escherichia\*  | -0.07 ± +0.85 | +0.15 ± +0.18 | 0.9977793 | 0.8317909 |  |  |
| Eubacterium | +0.09 ± +0.04 | +0.04 ± +0.04 | 0.1714168 | 0.6217228 |  |  |
| Eubacterium\*  | +0.07 ± +0.08 | +0.05 ± +0.07 | 0.8046785 | 0.8749758 |  |  |
| Faecalibacterium  | +0.01 ± +0.05 | -0.02 ± +0.04 | 0.9977793 | 0.9485637 |  |  |
| Faecalicatena | -0.01 ± +0.03 | -0.02 ± +0.03 | 0.9977793 | 0.9360358 |  |  |
| Faecalicoccus | -0.04 ± +0.07 | -0.14 ± +0.06 | 0.8775415 | 0.1368245 |  |  |
| Faecalitalea  | +0.01 ± +0.06 | -0.02 ± +0.05 | 0.9977793 | 0.9588657 |  |  |
| Fournierella  | -0.02 ± +0.03 | -0.02 ± +0.03 | 0.855962 | 0.8792838 |  |  |
| Gordonibacter | -0.12 ± +0.07 | +0.06 ± +0.06 | 0.2745007 | 0.6886612 |  |  |
| Haemophilus | -0.27 ± +0.14 | -0.14 ± +0.12 | 0.2512203 | 0.6091587 |  |  |
| Halapricum  | -0.08 ± +0.10 | -0.10 ± +0.08 | 0.8046785 | 0.6019557 |  |  |
| Holdemanella  | -0.04 ± +0.10 | +0.06 ± +0.09 | 0.9977793 | 0.8792838 |  |  |
| Holdemania  | -0.13 ± +0.08 | -0.10 ± +0.07 | 0.3630397 | 0.3653278 |  |  |
| **Hungatella**  | -0.29 ± +0.07 | -0.27 ± +0.06 | 0.0004967 | 0.000091 | \*\*\* | \*\*\* |
| Intestinibacter | -0.16 ± +0.11 | +0.08 ± +0.10 | 0.451381 | 0.8317909 |  |  |
| Johnsonella | -0.04 ± +0.04 | -0.06 ± +0.04 | 0.6851938 | 0.3183631 |  |  |
| Klebsiella  | -0.10 ± +1.25 | +0.01 ± +1.16 | 0.9977793 | 0.9986098 |  |  |
| Klebsiella\* | +0.03 ± +0.88 | +0.02 ± +0.76 | 0.9977793 | 0.9986098 |  |  |
| Kluyvera  | -0.47 ± +0.16 | +0.19 ± +0.14 | 0.043117 | 0.5134366 | \* |  |
| Lachnoanaerobaculum | -0.01 ± +0.04 | -0.03 ± +0.03 | 0.9977793 | 0.8317909 |  |  |
| Lachnoclostridium | -0.23 ± +0.06 | -0.11 ± +0.05 | 0.0004967 | 0.1368245 | \*\*\* |  |
| **Lactobacillus** | +0.26 ± +0.11 | +0.26 ± +0.10 | 0.1478217 | 0.043436 |  | \* |
| **Lactococcus** | +0.66 ± +0.13 | +0.44 ± +0.11 | 0.0000099 | 0.0011718 | \*\*\* | \*\* |
| Marvinbryantia  | +0.02 ± +0.04 | +0.00 ± +0.04 | 0.9086224 | 0.9986098 |  |  |
| Megamonas | +0.01 ± +1.36 | +0.07 ± +1.20 | 0.9977793 | 0.9986098 |  |  |
| Megasphaera | +0.05 ± +0.43 | +0.56 ± +0.12 | 0.9977793 | 0.0000342 |  | \*\*\* |
| Methanobrevibacter  | -0.16 ± +0.71 | -0.10 ± +0.62 | 0.9977793 | 0.9986098 |  |  |
| Methanomassiliicoccus | +0.09 ± +1.21 | +0.02 ± +1.07 | 0.9977793 | 0.9986098 |  |  |
| **Mitsuokella** | +1.13 ± +0.15 | +0.91 ± +0.13 | 0 | 0 | \*\*\* | \*\*\* |
| Odoribacter | -0.10 ± +0.08 | -0.12 ± +0.07 | 0.5811723 | 0.3183631 |  |  |
| Oscillibacter | -0.03 ± +0.05 | -0.02 ± +0.04 | 0.9085186 | 0.9485637 |  |  |
| Parabacteroides | -0.22 ± +0.09 | -0.22 ± +0.08 | 0.1206463 | 0.0390585 |  | \* |
| Paraprevotella  | -0.28 ± +0.12 | -0.21 ± +0.10 | 0.1471084 | 0.1709622 |  |  |
| Parasutterella  | -0.13 ± +0.15 | -0.21 ± +0.13 | 0.8046785 | 0.349507 |  |  |
| Phascolarctobacterium | +0.03 ± +0.12 | -0.03 ± +0.11 | 0.9977793 | 0.9986098 |  |  |
| Phocea  | -0.10 ± +0.05 | -0.11 ± +0.04 | 0.2272609 | 0.0611781 |  |  |
| Porphyromonas | -0.06 ± +0.07 | -0.04 ± +0.06 | 0.8046785 | 0.8696827 |  |  |
| Prevotella  | +0.03 ± +0.14 | +0.01 ± +0.12 | 0.9977793 | 0.9986098 |  |  |
| Roseburia | +0.04 ± +0.06 | +0.02 ± +0.05 | 0.8775415 | 0.9876269 |  |  |
| Ruminiclostridium | -0.14 ± +0.09 | -0.04 ± +0.08 | 0.4097612 | 0.9417014 |  |  |
| Ruminococcus  | +0.10 ± +0.06 | +0.08 ± +0.05 | 0.3321283 | 0.3653278 |  |  |
| Ruthenibacterium  | -0.30 ± +0.08 | -0.24 ± +0.07 | 0.0047908 | 0.009234 | \*\* | \*\* |
| **Sanguibacteroides** | -0.26 ± +0.10 | -0.30 ± +0.08 | 0.0699014 | 0.0030336 |  | \*\* |
| **Sellimonas**  | -0.01 ± +0.28 | +0.89 ± +0.08 | 0.9977793 | 0 |  | \*\*\* |
| Senegalimassilia  | -0.04 ± +0.09 | +0.04 ± +0.08 | 0.936578 | 0.9485637 |  |  |
| Shigella  | -0.10 ± +0.85 | +0.02 ± +0.75 | 0.9977793 | 0.9986098 |  |  |
| Solobacterium | +0.09 ± +0.08 | +0.16 ± +0.07 | 0.6215633 | 0.1525482 |  |  |
| Streptococcus | +0.01 ± +0.35 | +0.01 ± +0.30 | 0.9977793 | 0.9986098 |  |  |
| Subdoligranulum | +0.02 ± +0.03 | -0.02 ± +0.03 | 0.8595275 | 0.8317909 |  |  |
| Sutterella  | -0.13 ± +0.14 | -0.05 ± +0.12 | 0.7685222 | 0.9485637 |  |  |
| Tannerella  | -0.04 ± +0.09 | -0.06 ± +0.07 | 0.936578 | 0.8317909 |  |  |
| Turicibacter  | +0.02 ± +0.14 | -0.05 ± +0.12 | 0.9977793 | 0.9485637 |  |  |
| **Tyzzerella**  | -0.30 ± +0.06 | -0.30 ± +0.05 | 0.0000071 | 0.0000002 | \*\*\* | \*\*\* |
| Veillonella | +0.12 ± +0.48 | +0.08 ± +0.42 | 0.9977793 | 0.9986098 |  |  |

Sensitivity analyses where (1) follow-up limited to 7.5 years or (2) leisure activity and food choices covariates are included in the model. Genera that were significantly associated with incident AF in the main analyses are indicated using bold font weight. \*\*\*p<0.001; \*\*p<0.01; \*p<0.05.

**Supplementary Table 6.** Functional analysis for 6843 KEGG Orthology groups and AF after FDR-correction using Cox proportional hazard models

| **Term** | **Estimate** | **SE** | **Statistic** | **P value** | **FDR corrected P value** |  | **95% confidence interval** | **Mean confidence interval** | **Definition** | **Pathway** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| K00213 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | 7-dehydrocholesterol reductase | Steroid biosynthesis, Metabolic pathways, Biosynthesis of secondary metabolites |
| K00559 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | sterol 24-C-methyltransferase | Steroid biosynthesis, Metabolic pathways, Biosynthesis of secondary metabolites |
| K01399 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | pseudolysin | Cationic antimicrobial peptide (CAMP) resistance, Quorum sensing |
| K01401 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | aureolysin | Cationic antimicrobial peptide (CAMP) resistance, Staphylococcus aureus infection |
| K02919 | 0.1009882 | 0.0443427 | 2.277449 | 0.0227595 | 0.9989732 |  | 0.0140781 | 0.1878983 | 0.10 (0.01 to 0.19) | large subunit ribosomal protein L36 | Ribosome |
| K03220 | -0.0980878 | 0.0444199 | -2.208192 | 0.0272309 | 0.9989732 |  | -0.1851492 | -0.0110263 | -0.10 (-0.19 to -0.01) | type III secretion protein D |  |
| K03456 | 0.0680920 | 0.0338212 | 2.013293 | 0.0440838 | 0.9989732 |  | 0.0018036 | 0.1343803 | 0.07 (0.00 to 0.13) | serine/threonine-protein phosphatase 2A regulatory subunit A | mRNA surveillance pathway, Sphingolipid signaling pathway, Cell cycle - yeast, Meiosis - yeast, Oocyte meiosis, PI3K-Akt signaling pathway, AMPK signaling pathway, Adrenergic signaling in cardiomyocytes, TGF-beta signaling pathway, Hippo signaling pathway, Hippo signaling pathway - fly, Tight junction, Dopaminergic synapse, Long-term depression, Chagas disease, Hepatitis C, Human papillomavirus infection |
| K03941 | 0.0688739 | 0.0340109 | 2.025050 | 0.0428622 | 0.9989732 |  | 0.0022136 | 0.1355341 | 0.07 (0.00 to 0.14) | NADH dehydrogenase (ubiquinone) Fe-S protein 8 | Oxidative phosphorylation, Metabolic pathways, Thermogenesis, Retrograde endocannabinoid signaling, Non-alcoholic fatty liver disease, Alzheimer disease, Parkinson disease, Amyotrophic lateral sclerosis, Huntington disease, Prion disease, Pathways of neurodegeneration - multiple diseases |
| K04086 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | ATP-dependent Clp protease ATP-binding subunit ClpL |  |
| K04478 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | monofunctional glycosyltransferase | Peptidoglycan biosynthesis, Metabolic pathways |
| K05338 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | holin-like protein | Two-component system |
| K05339 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | holin-like protein LrgB | Two-component system |
| K05362 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | UDP-N-acetylmuramoyl-L-alanyl-D-glutamate-L-lysine ligase | Peptidoglycan biosynthesis, Metabolic pathways |
| K05817 | -0.0886165 | 0.0438368 | -2.021507 | 0.0432273 | 0.9989732 |  | -0.1745351 | -0.0026979 | -0.09 (-0.17 to -0.00) | LysR family transcriptional regulator, hca operon transcriptional activator |  |
| K06047 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | tubulin—tyrosine ligase |  |
| K07097 | 0.0790348 | 0.0397636 | 1.987618 | 0.0468540 | 0.9989732 |  | 0.0010996 | 0.1569700 | 0.08 (0.00 to 0.16) | uncharacterized protein |  |
| K07271 | 0.0892090 | 0.0435987 | 2.046139 | 0.0407427 | 0.9989732 |  | 0.0037571 | 0.1746608 | 0.09 (0.00 to 0.17) | lipopolysaccharide cholinephosphotransferase |  |
| K07681 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | two-component system, NarL family, vancomycin resistance sensor histidine kinase VraS | Two-component system |
| K07694 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | two-component system, NarL family, vancomycin resistance associated response regulator VraR | Two-component system |
| K08717 | 0.0920480 | 0.0419705 | 2.193157 | 0.0282961 | 0.9989732 |  | 0.0097872 | 0.1743087 | 0.09 (0.01 to 0.17) | urea transporter |  |
| K09130 | -0.0942641 | 0.0455712 | -2.068503 | 0.0385928 | 0.9989732 |  | -0.1835819 | -0.0049462 | -0.09 (-0.18 to -0.00) | uncharacterized protein |  |
| K09146 | -0.0889511 | 0.0437969 | -2.030990 | 0.0422560 | 0.9989732 |  | -0.1747915 | -0.0031107 | -0.09 (-0.17 to -0.00) | uncharacterized protein |  |
| K09813 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | hemin transport system permease protein | ABC transporters |
| K10850 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | MFS transporter, NNP family, putative nitrate transporter | Two-component system |
| K11442 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | putative uridylyltransferase |  |
| K11694 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | peptidoglycan pentaglycine glycine transferase (the second and third glycine) | Peptidoglycan biosynthesis, Metabolic pathways |
| K11695 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | peptidoglycan pentaglycine glycine transferase (the fourth and fifth glycine) | Peptidoglycan biosynthesis, Metabolic pathways |
| K12205 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | defect in organelle trafficking protein DotD |  |
| K12206 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | intracellular multiplication protein IcmB |  |
| K12213 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | intracellular multiplication protein IcmK |  |
| K12552 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | penicillin-binding protein 1 | Peptidoglycan biosynthesis, Metabolic pathways, beta-Lactam resistance |
| K12992 | 0.1040008 | 0.0442774 | 2.348845 | 0.0188318 | 0.9989732 |  | 0.0172186 | 0.1907829 | 0.10 (0.02 to 0.19) | rhamnosyltransferase | Biofilm formation - Pseudomonas aeruginosa |
| K13532 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | two-component system, sporulation sensor kinase D | Two-component system |
| K14088 | 0.0873584 | 0.0437240 | 1.997952 | 0.0457219 | 0.9989732 |  | 0.0016610 | 0.1730558 | 0.09 (0.00 to 0.17) | ech hydrogenase subunit C |  |
| K14467 | 0.0779259 | 0.0339558 | 2.294924 | 0.0217375 | 0.9989732 |  | 0.0113738 | 0.1444780 | 0.08 (0.01 to 0.14) | 4-hydroxybutyrate—CoA ligase (AMP-forming) | Carbon fixation pathways in prokaryotes, Metabolic pathways, Microbial metabolism in diverse environments, Carbon metabolism |
| K15060 | 0.0998319 | 0.0433328 | 2.303842 | 0.0212315 | 0.9989732 |  | 0.0149012 | 0.1847625 | 0.10 (0.01 to 0.18) | 5,5’-dehydrodivanillate O-demethylase oxygenase subunit | Aminobenzoate degradation, Microbial metabolism in diverse environments |
| K15566 | -0.0940566 | 0.0444014 | -2.118326 | 0.0341475 | 0.9989732 |  | -0.1810816 | -0.0070315 | -0.09 (-0.18 to -0.01) | tRNA (adenine9-N1/guanine9-N1)-methyltransferase |  |
| K15896 | 0.0909941 | 0.0393919 | 2.309970 | 0.0208898 | 0.9989732 |  | 0.0137874 | 0.1682008 | 0.09 (0.01 to 0.17) | UDP-4-amino-4,6-dideoxy-N-acetyl-beta-L-altrosamine N-acetyltransferase | Amino sugar and nucleotide sugar metabolism, O-Antigen nucleotide sugar biosynthesis, Metabolic pathways |
| K15897 | 0.0789413 | 0.0382919 | 2.061568 | 0.0392489 | 0.9989732 |  | 0.0038906 | 0.1539920 | 0.08 (0.00 to 0.15) | UDP-2,4-diacetamido-2,4,6-trideoxy-beta-L-altropyranose hydrolase | Amino sugar and nucleotide sugar metabolism, O-Antigen nucleotide sugar biosynthesis, Metabolic pathways |
| K15899 | 0.0789413 | 0.0382919 | 2.061568 | 0.0392489 | 0.9989732 |  | 0.0038906 | 0.1539920 | 0.08 (0.00 to 0.15) | pseudaminic acid cytidylyltransferase | Amino sugar and nucleotide sugar metabolism, O-Antigen nucleotide sugar biosynthesis, Metabolic pathways |
| K15913 | 0.0789413 | 0.0382919 | 2.061568 | 0.0392489 | 0.9989732 |  | 0.0038906 | 0.1539920 | 0.08 (0.00 to 0.15) | UDP-N-acetylbacillosamine N-acetyltransferase | Amino sugar and nucleotide sugar metabolism, Metabolic pathways |
| K16323 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | purine nucleoside transport protein |  |
| K17476 | -0.0912883 | 0.0434652 | -2.100262 | 0.0357058 | 0.9989732 |  | -0.1764785 | -0.0060981 | -0.09 (-0.18 to -0.01) | pentalenolactone synthase | Biosynthesis of various secondary metabolites - part 1, Metabolic pathways, Biosynthesis of secondary metabolites |
| K17624 | 0.0914296 | 0.0409557 | 2.232403 | 0.0255883 | 0.9989732 |  | 0.0111579 | 0.1717013 | 0.09 (0.01 to 0.17) | endo-alpha-N-acetylgalactosaminidase |  |
| K17641 | 0.0841197 | 0.0399690 | 2.104626 | 0.0353239 | 0.9989732 |  | 0.0057820 | 0.1624574 | 0.08 (0.01 to 0.16) | beta-xylosidase |  |
| K18290 | 0.0887504 | 0.0429206 | 2.067781 | 0.0386606 | 0.9989732 |  | 0.0046276 | 0.1728732 | 0.09 (0.00 to 0.17) | itaconyl-CoA hydratase | C5-Branched dibasic acid metabolism, Metabolic pathways |
| K18802 | 0.0663102 | 0.0332062 | 1.996922 | 0.0458336 | 0.9989732 |  | 0.0012272 | 0.1313932 | 0.07 (0.00 to 0.13) | glutamine amidotransferase |  |
| K18900 | 0.0915403 | 0.0443139 | 2.065724 | 0.0388546 | 0.9989732 |  | 0.0046866 | 0.1783939 | 0.09 (0.00 to 0.18) | LysR family transcriptional regulator, regulator for bpeEF and oprC |  |
| K18906 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | MarR family transcriptional regulator, multiple gene regulator MgrA |  |
| K18940 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | two-component system, OmpR family, sensor histidine kinase ArlS | Two-component system |
| K18941 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | two-component system, OmpR family, response regulator ArlR | Two-component system |
| K19668 | -0.0897443 | 0.0438306 | -2.047527 | 0.0406063 | 0.9989732 |  | -0.1756507 | -0.0038379 | -0.09 (-0.18 to -0.00) | cellulose 1,4-beta-cellobiosidase | Starch and sucrose metabolism, Metabolic pathways, Two-component system |
| K19975 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | manganese transport system substrate-binding protein | ABC transporters |
| K20338 | 0.0798183 | 0.0387872 | 2.057853 | 0.0396042 | 0.9989732 |  | 0.0037968 | 0.1558399 | 0.08 (0.00 to 0.16) | MarR family transcriptional regulator, global regulator for virulence | Quorum sensing |
| K20772 | 0.0914296 | 0.0409557 | 2.232403 | 0.0255883 | 0.9989732 |  | 0.0111579 | 0.1717013 | 0.09 (0.01 to 0.17) | 1-aminocyclopropane-1-carboxylate synthase 1/2/6 | Cysteine and methionine metabolism, Metabolic pathways, Biosynthesis of secondary metabolites, MAPK signaling pathway - plant |

AF stands for atrial fibrillation; SE stands for standard error