Supporting Information

**Liquid Biopsy for Patient Characterization in Cardiovascular Disease: Verification against Markers of Cytochrome P450 and P-Glycoprotein Activities**

Brahim Achour, Pauline Gosselin, Jean Terrier, Yvonne Gloor, Zubida M. Al-Majdoub, Thomas M. Polasek, Youssef Daali, Amin Rostami-Hodjegan, Jean-Luc Reny

\*Correspondence to: Dr B Achour; email: brahim.achour@manchester.ac.uk

**Supporting Information Content**

**Table S1.** Demographic and clinical details of plasma donors in the CVD cohort.

**Table S2.** Results of blood tests for the plasma donors in the CVD cohort.

**Table S3*.*** Demographic information of healthy plasma donors.

**Table S4.** dbSNP reference SNP (rs) numbers and gene sequence variations related to the polymorphisms of CYPs 1A2, 2B6, 2C9, 2C19, 2D6, 3A4 and 3A5 assessed in this study.

**Table S5.** Variant allele frequencies and predicted effect on phenotype.

**Table S6.** Expression levels of genes related to drug pharmacokinetics in liquid biopsy.

**Table S7.** Liquid biopsy expression of pharmacodynamic drug targets of medications received by the CVD cohort for the management of cardiovascular and related diseases.

**Figure S1.** Workflow ofliquid biopsy technology and assessment of liquid biopsy measurements in replicates of the CVD samples.

**Figure S2.** Concept and determination of exosomal shedding from liver into the bloodstream.

**Figure S3.** Covariates of shedding in the CVD cohort.

**Figure S4.** Correlation between concentration (ratio) and AUC (ratio) data measured using the Geneva cocktail.

**Figure S5.** Correlation between liquid biopsy replicate measurements and activity phenotype of CVD patient samples.

**Table S1.** Demographic and clinical details of plasma donors in the CVD cohort.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **Age***a* | **Sex** | **BMI****(kg/m2)** | **Ethnicity** | **Main diagnosis during index hospitalisation** | **Relevant medical history** | **Active inflammatory disease** | **Obesity** | **Alcohol (standard glasses/day)** | **Smoking** | **CYP inhibitors (< 7 d)** | **Date of blood sampling** |
| 1 | 66 | M | 21 | Caucasian | Acute heart failure | Lung cancer | yes | no | 1 | no | Esomeprazole | Aug2018 |
| 2 | 70 | M | 24 | Caucasian | VTE |  | no | no | 6 | yes |  | Aug2018 |
| 3 | 67 | M | 28 | Caucasian | Acute infection |  | no | no | 0 | yes | Ciprofloxacin | Aug2018 |
| 4 | 65 | M | 33 | Caucasian | Acute coronary syndrome |  | no | yes | 0 | no |  | Oct2018 |
| 5 | 62 | F | 33 | Caucasian | Ischemic stroke |  | no | yes | 12 | no |  | Oct2018 |
| 6 | 69 | M | 30 | Caucasian | Atrial fibrillation |  | no | no | - | no |  | Oct2018 |
| 7 | 60 | M | 28 | Caucasian | Acute coronary syndrome |  | no | no | 1 | yes | Esomeprazole | Nov2018 |
| 8 | 66 | M | 22 | Caucasian | Acute coronary syndrome |  | no | no | 0 | no | Clopidogrel | Dec2018 |
| 9 | 74 | M | 32 | Caucasian | Acute heart failure | Type 2 diabetes | no | no | 0 | no | Esomeprazole | Dec2018 |
| 10 | 70 | M | 41 | Caucasian | Acute coronary syndrome | Type 2 diabetes | no | yes | 0 | no | Clopidogrel, esomeprazole | Jan2019 |
| 11 | 61 | M | 26 | Caucasian | Acute infection | Type 2 diabetes | no | no | 0 | no |  | Jan2019 |
| 12 | 60 | F | 31 | Caucasian | VTE |  | no | yes | 0 | no |  | Feb2019 |
| 13 | 69 | M | 29 | Caucasian | COPD exacerbation | Type 2 diabetes, prostate cancer, cirrhosis | no | no | 0 | no | Clopidogrel | Feb2019 |
| 14 | 67 | M | 30 | Caucasian | Hematologic cancer | Cirrhosis | no | no | 14 | no |  | Feb2019 |
| 15 | 67 | M | 35 | Caucasian | Unstable angina | Gastrointestinal cancer | no | no | 0 | no | Esomeprazole | Feb2019 |
| 16 | 60 | M | 32 | Caucasian | Acute coronary syndrome |  | no | yes | 1 | no | Esomeprazole | March2019 |
| 17 | 63 | M | 24 | Caucasian | VTE |  | no | no | 0 | no |  | March2019 |
| 18 | 73 | M | 23 | Caucasian | Acute coronary syndrome |  | no | no | 0 | no | Esomeprazole, amiodarone | March2019 |
| 19 | 60 | F | 23 | Caucasian | Pericardial effusion |  | yes | no | 0 | no | Esomeprazole | March2019 |
| 20 | 67 | M | 25 | Caucasian | Acute coronary syndrome |  | no | no | 0 | yes |  | April2019 |
| 21 | 69 | M | 25 | Caucasian | Acute heart failure |  | no | no | 3 | no | Clopidogrel | April2019 |
| 22 | 75 | M | 20 | Caucasian | Acute heart failure | Type 2 diabetes | no | no | 0 | no |  | April2019 |
| 23 | 60 | M | 27 | Caucasian | Acute coronary syndrome |  | no | no | 1 | yes | Esomeprazole | May2019 |
| 24 | 61 | M | 16 | Caucasian | Acute coronary syndrome |  | no | no | 4 | yes |  | June2019 |
| 25 | 61 | F | 25 | Caucasian | Syncope | Type 2 diabetes | no | no | 0 | yes |  | June2019 |
| 26 | 73 | F | 28 | Caucasian | VTE | Genito-urinary cancer | no | no | 0 | no | Esomeprazole | June2019 |
| 27 | 67 | F | 25 | Caucasian | Acute coronary syndrome |  | no | no | 1 | no | Esomeprazole | July2019 |
| 28 | 68 | M | 25 | Caucasian | Trans-catheter heart valve procedure |  | no | no | 2 | no | Clopidogrel, esomeprazole | Aug2019 |
| 29 | 70 | M | 26 | Caucasian | Acute heart failure | Prostate cancer | no | no | 8 | no | Clopidogrel | Aug2019 |
| 30 | 64 | F | 29 | Caucasian | Carotid artery stenting  |  | no | no | 0 | no | Clopidogrel | Sept2019 |

*a* Age (years) at blood collection; BMI, body mass index; COPD, chronic obstructive pulmonary disease; F, female; M, male; VTE, venous thromboembolism; - symbols represent missing information from patient records.

**Table S2.** Results of blood tests for the plasma donors in the CVD cohort.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **ASAT (U/L)** | **ALAT (U/L)** | **GGT (U/L)** | **ALP (U/L)** | **Bilirubin (µmol/L)** | **Creatinine (µmol/L)** | **Creatinine clearance** *a* **(mL/min)** | **eGFR** *b* **(mL/min/1.73 m2)** | **Albumin (g/L)** |
| 1 | 22 | 10 | 177 | 163 | 26 | 85 | 78.85 | 83 | 36 |
| 2 | 31 | 27 | 64 | 59 | 9 | 84 | 84 | 81 | 42 |
| 3 | 38 | 41 | 50 | 57 | 3 | 88 | 100.32 | 79 | 28 |
| 4 | 40 | 50 | 48 | 65 | 10 | 105 | 99.27 | 64 | 42 |
| 5 | 15 | 15 | 27 | 104 | 3 | 60 | 0.34 | 95 | 24 |
| 6 | 24 | 33 | 39 | 43 | 11 | 102 | 75.19 | 65 | 42 |
| 7 | 18 | 27 | 58 | 68 | 6 | 97 | 110.31 | 73 | 42 |
| 8 | 49 | 29 | 17 | 44 | 8 | 73 | 93.76 | 97 | 38 |
| 9 | 24 | 30 | 27 | 72 | 11 | 100 | 82.41 | 64 | 37 |
| 10 | 10 | 13 | 20 | 40 | 4 | 149 | 71.59 | 41 | 36 |
| 11 | 11 | 16 | 34 | 82 | 8 | 68 | 102.67 | 99 | 36 |
| 12 | 13 | 23 | 28 | 81 | 5 | 110 | 67.77 | 47 | 43 |
| 13 | 58 | 127 | 212 | 46 | <3 | 66 | 111.54 | 94 | 38 |
| 14 | 59 | 31 | 526 | 221 | 11 | 83 | 99.03 | 84 | 32 |
| 15 | 38 | 53 | 43 | 58 | 13 | 77 | 116.14 | 89 | 43 |
| 16 | 24 | 29 | 24 | 50 | 23 | 94 | 92.33 | 76 | 42 |
| 17 | 73 | 73 | 62 | 90 | 6 | 64 | 109.06 | 99 | 29 |
| 18 | 36 | 50 | 152 | 113 | 19 | 79 | 74.38 | 85 | 35 |
| 19 | 30 | 54 | 25 | 33 | 4 | 58 | 86.07 | 97 | 41 |
| 20 | 22 | 21 | 57 | 66 | 9 | 76 | 84.83 | 90 | 42 |
| 21 | 21 | 19 | 65 | 57 | 13 | 67 | 101.28 | 93 | 37 |
| 22 | 26 | 24 | 64 | 111 | 11 | 84 | 61.85 | 79 | 38 |
| 23 | 15 | 36 | 71 | 57 | 15 | 132 | 66.72 | 50 | 40 |
| 24 | 50 | 27 | 156 | 77 | 6 | 56 | 86.93 | 106 | 41 |
| 25 | 19 | 30 | 52 | 64 | 6 | 50 | 118.64 | 101 | 36 |
| 26 | 21 | 14 | 39 | 56 | 3 | 62 | 81.9 | 87 | 38 |
| 27 | 68 | 27 | 20 | 52 | 10 | 84 | 61.64 | 62 | 43 |
| 28 | 10 | 11 | 20 | 57 | 11 | 88 | 73.97 | 78 | 36 |
| 29 | 34 | 12 | 208 | 1406 | 17 | 96 | 77.87 | 69 | 35 |
| 30 | Hemolyzed | 15 | 16 | 50 | 7 | 74 | 68.69 | 74 | 34 |

ALAT, alanine aminotransferase; ALP, alkaline phosphatase; ASAT, aspartate aminotransferase; GGT, gamma-glutamyl transferase; - symbols represent missing information from patient records.

*a* Creatinine clearance was calculated using Cockcroft-Gault equation; *b* eGFR was calculated using the CKD-EPI equation.

**Table S3.** Demographic information of healthy plasma donors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Donor** | **Age** *a* | **Sex** | **Ethnicity** | **Diagnosis** | **Date of blood sampling** |
| 101 | 51 | M | Caucasian | Healthy | April2018 |
| 102 | 23 | F | Hispanic | Healthy | April2018 |
| 103 | 39 | F | Hispanic | Healthy  | April2018 |
| 104 | 53 | M | Black | Healthy  | April2018 |
| 105 | 57 | M | Caucasian | Healthy | April2018 |
| 106 | 41 | M | Hispanic | Healthy | April2018 |
| 107 | 53 | M | Caucasian | Healthy | April2018 |

*a* Age (years) at blood collection; F, female; M, male.

**Table S4.** dbSNP reference SNP (rs) numbers and gene sequence variations related to polymorphisms of CYPs 1A2, 2B6, 2C9, 2C19, 2D6, 3A4 and 3A5 assessed in this study.

|  |  |  |
| --- | --- | --- |
| **Gene** | **rs number** | **Gene sequence variation** |
| CYP1A2 | rs762551 | -163C>A |
|   | rs2069514 | -3860G>A |
|   | rs2069526 | -739T>G |
|   | rs12720461 | -729C>T |
|   | rs35694136 | -2467delT |
| CYP2B6 | rs28399499 | 21011T>C |
|   | rs34223104 | -82T>C |
|   | rs3211371 | 25505C>T |
| CYP2C9 | rs1799853 | 3608C>T |
|   | rs1057910 | 42614A>C  |
|   | rs28371686 | 42619C>G |
|   | rs9332131 | 10601delA |
|   | rs56165452 | 42615T>C |
|   | rs28371685 | 42542C>T |
| CYP2C19 | rs17884712 | 12784G>A |
|   | rs4244285 | 19154G>A |
|   | rs12248560 | -806C>T |
|   | rs72552267 | 12748G>A  |
|   | rs4986893 | 17948G>A |
|   | rs56337013 | 90033C>T |
|   | rs72558186 | 19294T>A |
|   | rs6413438 | 19153C>T |
|   | rs41291556 | 12711T>C |
|   | rs28399504 | 1A>G |
| CYP2D6 | rs28371706 | 1023C>T |
|   | rs1065852 | 100C>T |
|   | rs1135840 | 4180G>C |
|   | rs16947 | 2850C>T |
|   | rs3892097 | 1846G>A |
|   | rs5030862 | 124G>A  |
|   | rs5030867 | 2935A>C |
|   | rs5030656 | 2615\_2617delAAG |
|   | rs35742686 | 2549delA |
|   | rs5030655 | 1707delT |
|   | rs59421388 | 3183G>A |
|   | rs28371725 | 2988G>A |
|   | rs5030865 | 1758G>T |
|   | cnv\_exon 9 | 1, 2 or 3 copies |
| CYP3A4 | rs2740574 | -392A>G |
|   | rs4987161 | 15624T>C |
|   | rs12721629 | 21905C>T  |
|   | rs55785340 | 15722T>C |
|   | rs35599367 | 15389C>T (intronic) |
|   | rs4986910 | 23181T>C  |
| CYP3A5 | rs10264272 | 14685G>A |
|   | rs28365083 | 27284C>A |
|   | rs28383479 | 19381G>A |
|   | rs28383468 | 3705C>T |
|   | rs55817950 | 3699C>T |
|   | rs776746 | 6981A>G |
|   | rs41303343 | 27126\_27127insT |

rs, reference SNP; SNP, single nucleotide polymorphism; snv, sequence number variation; del, deletion; ins, insertion.

**Table S5.** Variant allele frequencies and predicted effect on phenotype.

|  |  |  |  |
| --- | --- | --- | --- |
| **Enzymes and variant alleles** | **% of study cohort (*n*)** | **Samples** | **Predicted activity phenotype** |
| **CYP1A2** |   |  |   |
| \*1A/\*1A | 10% (3) | 15, 24, 30 | NM |
| \*1A/\*1F | 50% (15) | 1, 3, 5, 7, 8, 11, 12, 16, 17, 19, 22, 25, 26, 27, 29 | Hyper-inducer |
| \*1F/\*1F | 30% (9) | 2, 4, 9, 13, 14, 18, 20, 21, 23 | Hyper-inducer |
| Other \*1/\*1 (C/D/F/K) | 10% (3) | 6, 10, 28 | - |
| **CYP2B6** |   |  |   |
| \*1/\*1 | 83.3% (25) | All except samples with \*1/\*5, \*1/\*22 or \*5/\*5 genotype | NM |
| \*1/\*5 | 10% (3) | 7, 11, 23 | NM, no change in function  |
| \*1/\*22 | 3.3% (1) | 9 | RM, increased function  |
| \*5/\*5 | 3.3% (1) | 13 | NM, no change  |
| **CYP2C9** |   |  |   |
| \*1/\*1 | 66.7% (20) | All except samples with \*1/\*2, \*1/\*3 or \*2/\*3 genotype | NM  |
| \*1/\*2 | 16.7% (5) | 1, 7, 8, 11, 18 | IM, reduced function |
| \*1/\*3 | 13.3% (4) | 2, 12, 15, 27 | IM, reduced function  |
| \*2/\*3 | 3.3% (1) | 22 | PM, reduced function  |
| **CYP2C19** |   |  |   |
| \*1/\*1 | 40% (12) | 6, 8, 10, 12, 15, 17, 18, 22, 23, 26, 27, 29 | NM |
| \*1/\*2 | 13.3% (4) | 7, 13, 16, 24 | IM, reduced function |
| \*1/\*17 | 36.7% (11) | 1, 2, 3, 4, 5, 9, 11, 19, 21, 25, 30 | RM, increased function  |
| \*2/\*17 | 6.7% (2) | 14, 28 | IM, reduced function |
| ND *a* | 3.3% (1) | 20 | - |
| **CYP2D6**  |   |  |   |
| \*1/\*1 | 26.7% (8) | 3, 6, 9, 11, 18, 21, 23, 25 | NM (AS = 2) |
| \*1/\*2 | 13.3% (4) | 2, 12, 14, 29 | NM (AS = 2) |
| \*1/\*4 | 6.7% (2) | 7, 20 | IM (AS = 1) |
| \*1/\*41 | 13.3% (4) | 4, 5, 13, 19 | NM (AS = 1.5) |
| \*2/\*2 | 10% (3) | 16, 22, 27 | NM (AS = 2) |
| \*2/\*2x2 | 3.3% (1) | 10 | UM (AS = 3) |
| \*2/\*4 | 6.7% (2) | 17, 26 | IM (AS = 1) |
| \*2/\*5 | 3.3% (1) | 28 | IM (AS = 1) |
| \*2/\*9 | 3.3% (1) | 1 | NM (AS = 1.5) |
| \*4/\*41 | 3.3% (1) | 30 | IM (AS = 0.5) |
| ND *a* | 10% (3) | 8, 15, 24 | - |
| **CYP3A4** |   |  |   |
| \*1/\*1 | 93.3% (28) | All except samples with \*1/\*22 genotype | NM |
| \*1/\*22 | 6.7% (2) | 2, 20 | Reduced function  |
| **CYP3A5** |   |  |   |
| \*1/\*3 | 10% (3) | 5, 7, 23 | IM, reduced function |
| \*3/\*3 | 90% (27) | All except samples with \*1/\*3 genotype | PM, inactive  |

*a* Genotype of CYP2C19 and CYP2D6 was not determined in 1 and 3 donors, respectively.

AS, activity score; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM/UM, rapid/ultra-rapid metabolizer.

**Table S6.** Expression levels of targets related to drug pharmacokinetics in liquid biopsy. Expression levels above the limit of quantification were normalized to the total number of reads in each sample.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene name** | **Tissue***a* | **Mean (RPM)***b* | **SD***b* | ***n****b* | **FC***c* |  | **Gene name** | **Tissue***a* | **Mean (RPM)***b* | **SD***b* | ***n****b* | **FC***c* |
| AADAC | LI | 0.44 | 0.30 | 11 | 1.96 |  | CYP4Z1 | PSL | 0.53 | 0.56 | 20 | 0.97 |
| AKR1A1 | KIL | 32.19 | 8.29 | 25 | 0.85 |  | CYP51A1 | LPGi | 35.26 | 16.16 | 25 | 1.69 |
| AKR1B1 | A | 18.28 | 5.14 | 25 | 0.52 |  | **CYP7A1** | **L** | **0.33** | **0.61** | **5** | **5.45** |
| **AKR1B10** | **Gi** | **0.17** | **0.15** | **6** | **0.37** |  | CYP7B1 | - | 0.57 | 0.54 | 15 | 0.55 |
| AKR1C1 | L | 2.32 | 1.45 | 25 | 0.68 |  | CYP8B1 | L | 10.53 | 6.72 | 25 | 1.18 |
| **AKR1C2** | **L** | **2.79** | **1.76** | **25** | **0.45** |  | DHFR | GiLK | 63.47 | 30.74 | 25 | 1.63 |
| AKR1C3 | IKL | 10.23 | 4.68 | 25 | 0.66 |  | DHFRL1 | - | 0.20 | 0.11 | 16 | 0.77 |
| AKR1C4 | L | 0.54 | 0.63 | 16 | 1.93 |  | EPHX1 | LA | 3.99 | 1.89 | 25 | 0.82 |
| AKR1D1 | L | 0.51 | 0.63 | 17 | 1.53 |  | EPHX2 | IL | 10.15 | 5.18 | 25 | 1.01 |
| AKR1E2 | T | 10.77 | 8.88 | 25 | 0.72 |  | EPHX3 | SGi | 0.59 | 1.05 | 10 | 1.30 |
| AKR7A2 | KIL | 25.50 | 10.66 | 25 | 1.13 |  | **EPHX4** | **B** | **0.55** | **0.44** | **15** | **2.80** |
| AKR7A3 | IKL | 0.80 | 0.96 | 19 | 1.10 |  | ESD | - | 9.39 | 4.80 | 25 | 0.58 |
| ALDH16A1 | GiKL | 37.36 | 8.04 | 25 | 0.93 |  | FMO2 | PL | 4.39 | 3.28 | 25 | 1.44 |
| **ALDH1A1** | **LGi** | **3.33** | **1.50** | **25** | **0.43** |  | FMO3 | L | 0.47 | 0.44 | 18 | 0.64 |
| ALDH1A2 | GiKP | 2.96 | 1.94 | 25 | 0.74 |  | FMO4 | KL | 1.74 | 1.09 | 25 | 1.43 |
| ALDH1A3 | Pr | 0.15 | 0.13 | 25 | 1.56 |  | FMO5 | LI | 7.38 | 3.49 | 25 | 1.72 |
| ALDH1B1 | LKI | 1.58 | 0.86 | 25 | 0.96 |  | GGT1 | KIL | 1.27 | 0.99 | 22 | 1.92 |
| ALDH1L1 | LK | 0.22 | 0.22 | 10 | 1.11 |  | **GGT5** | **KGiL** | **0.92** | **0.67** | **19** | **2.94** |
| **ALDH1L2** | **Gi** | **0.66** | **0.72** | **17** | **3.43** |  | GGT7 | GiKL | 1.15 | 0.97 | 22 | 0.84 |
| ALDH2 | LKP | 70.52 | 37.25 | 25 | 1.18 |  | GGTLC2 | T | 1.40 | 0.90 | 18 | 1.27 |
| ALDH3A1 | Gi | 0.44 | 0.41 | 8 | 1.40 |  | GLYAT | KL | 0.61 | 0.79 | 14 | 1.72 |
| ALDH3A2 | SKL | 0.78 | 0.50 | 24 | 0.79 |  | **GLYATL1** | **KL** | **0.41** | **0.41** | **24** | **2.33** |
| ALDH3B1 | PK | 39.90 | 15.58 | 25 | 1.17 |  | **GLYATL2** | **BrU** | **5.02** | **18.30** | **25** | **3.66** |
| ALDH4A1 | KL | 2.74 | 1.83 | 25 | 1.10 |  | GLYATL3 | LI | 0.04 | 0.04 | 13 | 1.43 |
| ALDH5A1 | LBK | 12.79 | 8.97 | 25 | 0.92 |  | GPX1 | GiKLP | 1023.64 | 638.22 | 25 | 1.01 |
| ALDH6A1 | KL | 0.89 | 0.56 | 25 | 0.90 |  | GPX2 | L | 0.39 | 0.24 | 14 | 1.53 |
| ALDH7A1 | KLB | 4.44 | 2.96 | 25 | 0.58 |  | GPX3 | K | 6.82 | 3.16 | 25 | 0.72 |
| ALDH8A1 | LK | 0.09 | 0.07 | 9 | 1.03 |  | GPX4 | GiKL | 93.90 | 33.27 | 25 | 0.72 |
| ALDH9A1 | GiLK | 93.35 | 22.44 | 25 | 1.18 |  | **GPX7** | **GiKL** | **7.80** | **3.54** | **25** | **2.09** |
| **ALOX12** | **GiS** | **38.03** | **47.30** | **25** | **2.05** |  | GPX8 | GILK | 0.58 | 0.53 | 17 | 1.53 |
| **ALOX15** | **P** | **1.58** | **1.97** | **24** | **0.48** |  | GSTA1 | LKI | 0.48 | 0.45 | 23 | 0.80 |
| ALOX5 | P | 43.10 | 15.70 | 25 | 0.75 |  | GSTA4 | A | 5.55 | 2.59 | 25 | 0.81 |
| AOC2 | T | 0.37 | 0.35 | 19 | 0.83 |  | **GSTA5** | **LKT** | **0.03** | **0.01** | **3** | **-** |
| AOC3 | P | 2.70 | 1.90 | 24 | 1.48 |  | GSTM1 | LKI | 8.27 | 9.58 | 22 | 1.93 |
| AOX1 | LK | 1.12 | 1.36 | 23 | 1.61 |  | GSTM2 | GiLK | 3.44 | 2.50 | 25 | 0.80 |
| XDH | IL | 0.21 | 0.20 | 5 | 0.76 |  | GSTM3 | TKB | 3.49 | 3.02 | 25 | 1.21 |
| BAAT | L | 0.35 | 0.45 | 7 | 1.48 |  | GSTM4 | IKL | 8.96 | 5.54 | 25 | 1.00 |
| BCHE | L | 0.23 | 0.18 | 7 | 1.39 |  | GSTM5 | GiKB | 0.54 | 0.62 | 21 | 1.01 |
| BLVRA | GiPK | 35.48 | 19.40 | 25 | 0.62 |  | GSTP1 | GiPK | 302.05 | 76.95 | 25 | 0.94 |
| CES1 | L | 3.37 | 1.94 | 24 | 1.23 |  | **GSTT1** | **LGiBr** | **0.75** | **0.61** | **21** | **0.47** |
| CES2 | GiLK | 12.81 | 3.66 | 25 | 0.76 |  | GSTT2 | Br | 0.10 | 0.03 | 9 | 1.97 |
| CES3 | GiLK | 0.37 | 0.53 | 3 | 1.75 |  | **GSTT2B** | **Br** | **0.33** | **0.33** | **21** | **2.29** |
| **CHDH** | **KL** | **0.58** | **0.62** | **19** | **7.40** |  | **IL4I1** | **LGi** | **5.03** | **4.89** | **25** | **2.58** |
| COMT | L | 17.64 | 5.94 | 25 | 1.15 |  | LOXL2 | GiLK | 0.81 | 0.52 | 23 | 0.85 |
| CYP11A1 | A | 0.67 | 0.63 | 15 | 1.28 |  | **LOXL3** | **GiKL** | **1.95** | **1.82** | **23** | **2.52** |
| CYP11B1 | A | 1.66 | 1.37 | 25 | 1.12 |  | **LOXL4** | **KGiL** | **0.42** | **0.45** | **6** | **4.75** |
| CYP17A1 | A | 0.09 | 0.14 | 3 | 1.84 |  | LTA4H | - | 158.85 | 46.48 | 25 | 0.98 |
| **CYP19A1** | **Pl** | **0.46** | **0.35** | **5** | **2.54** |  | MAOA | - | 4.19 | 2.62 | 25 | 1.00 |
| CYP1A1 | LI | 5.94 | 5.09 | 24 | 1.90 |  | **MAOB** | **LKI** | **7.00** | **8.88** | **25** | **3.05** |
| CYP1A2*d* | L | 0.65 | 0.59 | 10 | 0.87 |  | MGST1 | LKI | 12.50 | 9.53 | 25 | 1.68 |
| CYP1B1 | PL | 7.40 | 5.33 | 25 | 0.62 |  | MGST2 | LIK | 7.76 | 3.75 | 18 | 0.56 |
| CYP20A1 | - | 18.01 | 6.41 | 25 | 1.13 |  | MGST3 | ILK | 147.13 | 61.49 | 25 | 1.47 |
| CYP24A1 | KPl | 0.86 | 0.99 | 3 | 1.88 |  | **NAT2** | **LI** | **0.22** | **0.18** | **4** | **2.28** |
| **CYP26A1** | **L** | **0.45** | **0.47** | **5** | **2.34** |  | NDOR1 | GiKL | 9.13 | 3.47 | 25 | 1.20 |
| CYP26B1 | TSBK | 0.49 | 0.41 | 25 | 0.92 |  | POR | L | 2.80 | 1.34 | 25 | 0.75 |
| CYP26C1 | BGi | 0.15 | 0.26 | 4 | 0.86 |  | **SULT1A1** | **L** | **0.64** | **1.21** | **9** | **2.04** |
| CYP27A1 | L | 5.13 | 2.32 | 25 | 0.96 |  | SULT1A2 | IL | 0.39 | 0.53 | 21 | 1.71 |
| CYP27B1 | K | 0.32 | 0.23 | 8 | 0.97 |  | SULT1A4 | I | 4.82 | 1.66 | 18 | 0.66 |
| CYP2A13 | L | 0.04 | 0.02 | 8 | 1.19 |  | SULT1B1 | I | 17.46 | 10.14 | 25 | 1.12 |
| CYP2A6 | L | 0.35 | 0.49 | 6 | 1.39 |  | **SULT1C2** | **KGi** | **0.13** | **0.08** | **4** | **0.30** |
| CYP2B6*d* | LK | 0.69 | 0.58 | 24 | 1.26 |  | SULT1C4 | - | 1.19 | 0.84 | 24 | 0.97 |
| **CYP2C18** | **LGi** | **1.05** | **1.42** | **12** | **3.67** |  | **SULT2A1** | **L** | **1.03** | **1.02** | **22** | **2.10** |
| **CYP2C19*d*** | **LI** | **1.42** | **1.01** | **7** | **3.75** |  | SULT2B1 | SGi | 0.68 | 0.80 | 16 | 1.36 |
| CYP2C8 | L | 0.09 | 0.12 | 15 | 1.25 |  | TPMT | KLTh | 18.47 | 6.17 | 25 | 0.64 |
| CYP2C9*d* | LI | 2.88 | 2.83 | 24 | 1.39 |  | UGT1A8 | I | 16.60 | 12.09 | 25 | 1.58 |
| **CYP2D6*d*** | **LI** | **0.35** | **0.11** | **4** | **2.22** |  | **UGT2B10** | **L** | **0.42** | **0.35** | **4** | **4.37** |
| CYP2E1 | L | 5.73 | 5.74 | 25 | 0.77 |  | UGT2B11 | L | 0.10 | 0.08 | 5 | 0.70 |
| **CYP2F1** | **PT** | **0.09** | **0.16** | **8** | **5.68** |  | **UGT2B15** | **LI** | **0.32** | **0.53** | **6** | **7.84** |
| **CYP2J2** | **LI** | **0.66** | **1.07** | **8** | **2.97** |  | **UGT2B17** | **IL** | **0.25** | **0.49** | **8** | **10.24** |
| CYP2R1 | - | 0.95 | 0.50 | 24 | 0.74 |  | UGT2B4 | L | 0.36 | 0.41 | 13 | 0.51 |
| CYP2S1 | Gi | 1.19 | 1.02 | 24 | 1.14 |  | UGT2B7 | LK  | 0.07 | 0.04 | 6 | 1.68 |
| CYP2U1 | - | 1.50 | 1.14 | 22 | 0.95 |  | **UGT3A1** | **KL** | **0.23** | **0.29** | **4** | **3.58** |
| **CYP2W1** | **GiS** | **0.07** | **0.06** | **12** | **3.32** |  | **UGT3A2** | **STK** | **0.35** | **0.39** | **16** | **4.81** |
| **CYP39A1** | **L** | **0.23** | **0.26** | **14** | **2.07** |  | ABCA1 | - | 1.95 | 1.49 | 25 | 1.67 |
| **CYP3A4*d*** | **LI** | **0.38** | **0.51** | **9** | **2.32** |  | **ABCA10** | **OGiL** | **0.65** | **0.73** | **7** | **5.26** |
| CYP3A5*d* | GiL | 0.35 | 0.25 | 8 | 1.09 |  | **ABCA13** | **BmPT** | **1.25** | **1.93** | **20** | **2.94** |
| CYP3A7*d* | LK | 0.32 | 0.23 | 4 | 0.62 |  | ABCA2 | B | 4.69 | 2.36 | 25 | 1.37 |
| **CYP46A1** | **B** | **0.22** | **0.21** | **6** | **5.61** |  | ABCA3 | BP | 2.86 | 2.22 | 25 | 1.75 |
| **CYP4A22** | **LK** | **0.99** | **0.87** | **3** | **14.61** |  | ABCA5 | SGiM | 1.61 | 1.13 | 24 | 1.17 |
| CYP4B1 | P | 0.21 | 0.22 | 14 | 0.85 |  | ABCA6 | LOP | 0.62 | 0.45 | 19 | 1.54 |
| CYP4F12 | ISL | 5.40 | 4.52 | 24 | 1.39 |  | ABCA7 | BmGi | 1.29 | 0.74 | 25 | 0.90 |
| CYP4F2 | LIK | 0.28 | 0.20 | 9 | 1.04 |  | ABCA8 | OPLK | 0.29 | 0.13 | 6 | 1.53 |
| CYP4F22 | SL | 0.06 | 0.04 | 12 | 1.58 |  | **ABCA9** | **OPLK** | **0.65** | **0.55** | **16** | **2.87** |
| **CYP4F3** | **LK** | **4.63** | **4.14** | **25** | **2.79** |  | **ABCB1*d*** | **LIK** | **27.69** | **24.27** | **25** | **2.09** |
| CYP4V2 | LKGi | 7.91 | 3.46 | 25 | 0.80 |  | ABCB10 | BmGi | 46.99 | 31.44 | 25 | 1.16 |
| **CYP4X1** | **U**  | **0.26** | **0.49** | **10** | **0.18** |   | **ABCB11** | **L** | **0.33** | **0.35** | **4** | **-** |

**Table S6.** Continued.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene name** | **Tissue***a* | **Mean (RPM)***b* | **SD***b* | **n***b* | **FC***c* |  | **Gene name** | **Tissue***a* | **Mean (RPM)***b* | **SD***b* | **n***b* | **FC***c* |
| ABCB4 | L | 0.83 | 0.48 | 24 | 0.52 |  | **SLC22A7** | **L** | **5.37** | **4.82** | **23** | **2.42** |
| ABCB5 | TR | 0.76 | 1.08 | 20 | 0.72 |  | **SLC23A1** | **IL** | **0.02** | **0.01** | **4** | **-** |
| ABCB6 | - | 3.56 | 2.81 | 24 | 0.73 |  | SLC23A2 | A | 1.76 | 0.97 | 25 | 0.63 |
| ABCB8 | - | 0.34 | 0.28 | 25 | 1.34 |  | **SLC23A3** | **IK** | **0.06** | **0.07** | **5** | **0.23** |
| ABCC1 | - | 10.28 | 3.24 | 25 | 0.80 |  | SLC24A1 | R | 4.38 | 2.73 | 25 | 1.24 |
| ABCC10 | - | 1.47 | 1.05 | 23 | 0.78 |  | SLC24A3 | - | 14.78 | 16.75 | 25 | 1.77 |
| ABCC13 | I | 27.69 | 19.18 | 25 | 1.59 |  | **SLC24A4** | **B** | **1.47** | **1.07** | **24** | **0.40** |
| ABCC2 | LIK | 0.27 | 0.20 | 11 | 1.33 |  | **SLC24A6** | **-** | **0.08** | **0.05** | **18** | **0.44** |
| ABCC3 | LGi | 6.48 | 7.72 | 25 | 2.00 |  | SLC25A1 | - | 53.25 | 14.18 | 25 | 0.87 |
| ABCC4 | PrKP | 7.10 | 7.91 | 25 | 0.58 |  | SLC25A10 | L | 0.75 | 0.63 | 18 | 0.84 |
| ABCC5 | GiBP | 1.53 | 1.12 | 25 | 0.53 |  | SLC25A11 | MHK | 98.15 | 23.55 | 25 | 1.38 |
| ABCC6 | LKI | 0.07 | 0.03 | 5 | 0.94 |  | **SLC25A12** | **MHB** | **1.41** | **0.89** | **25** | **0.47** |
| **ABCC9** | **LH** | **0.15** | **0.11** | **4** | **7.26** |  | SLC25A13 | L | 3.17 | 1.76 | 25 | 0.59 |
| ABCD1 | IT | 15.02 | 5.66 | 25 | 1.21 |  | **SLC25A14** | **-** | **0.44** | **0.56** | **4** | **5.85** |
| ABCD2 | BH | 4.34 | 2.32 | 24 | 1.25 |  | SLC25A15 | IL | 2.64 | 1.03 | 25 | 0.66 |
| ABCD3 | - | 17.21 | 6.11 | 25 | 0.87 |  | SLC25A16 | - | 22.91 | 8.51 | 25 | 1.12 |
| ABCD4 | - | 3.71 | 1.65 | 25 | 0.77 |  | SLC25A17 | - | 12.18 | 4.51 | 25 | 1.35 |
| ABCE1 | - | 110.13 | 22.93 | 25 | 1.35 |  | SLC25A18 | BL | 0.17 | 0.13 | 21 | 0.80 |
| ABCF1 | M | 10.48 | 2.26 | 18 | 1.07 |  | SLC25A19 | T | 12.19 | 4.69 | 25 | 1.17 |
| ABCF2 | - | 42.73 | 11.00 | 25 | 1.18 |  | SLC25A2 | T | 19.24 | 11.12 | 25 | 1.02 |
| ABCF3 | - | 42.23 | 8.12 | 25 | 1.43 |  | SLC25A20 | LI | 25.93 | 7.37 | 25 | 1.15 |
| ABCG1 | - | 0.35 | 0.26 | 21 | 0.62 |  | SLC25A21 | T | 0.53 | 0.78 | 22 | 0.66 |
| **ABCG2** | **LIB** | **13.36** | **9.26** | **25** | **2.42** |  | SLC25A22 | B | 15.73 | 6.51 | 25 | 1.21 |
| ABCG4 | BRT | 0.11 | 0.25 | 8 | 0.89 |  | SLC25A23 | B | 12.24 | 8.51 | 25 | 0.64 |
| **ABCG8** | **IL** | **0.21** | **0.08** | **4** | **3.18** |  | SLC25A24 | - | 32.30 | 7.38 | 25 | 1.12 |
| SLC10A3 | - | 10.92 | 7.12 | 25 | 1.10 |  | SLC25A25 | - | 10.61 | 4.21 | 25 | 1.09 |
| SLC10A4 | BA | 0.10 | 0.05 | 6 | 1.60 |  | SLC25A26 | - | 3.37 | 1.36 | 25 | 0.52 |
| SLC10A5 | BL | 30.42 | 19.24 | 25 | 1.64 |  | SLC25A28 | - | 8.53 | 2.71 | 25 | 0.97 |
| **SLC10A6** | **BrS** | **0.71** | **0.65** | **13** | **2.97** |  | SLC25A29 | Th | 3.98 | 3.46 | 25 | 1.00 |
| SLC10A7 | - | 5.52 | 3.83 | 25 | 1.02 |  | SLC25A3 | H | 149.42 | 31.55 | 25 | 0.72 |
| SLC11A1 | PBm | 6.35 | 2.25 | 25 | 0.73 |  | SLC25A30 | HM | 40.66 | 12.76 | 25 | 1.20 |
| **SLC11A2** | **-** | **1.99** | **1.43** | **23** | **4.04** |  | SLC25A32 | - | 23.69 | 5.67 | 25 | 0.75 |
| SLC12A2 | GiL | 3.01 | 1.99 | 25 | 0.52 |  | SLC25A33 | - | 36.90 | 21.53 | 25 | 1.24 |
| SLC12A3 | K | 0.27 | 0.19 | 23 | 0.97 |  | SLC25A35 | T | 4.91 | 2.47 | 25 | 1.19 |
| SLC12A4 | - | 1.73 | 0.60 | 25 | 0.84 |  | SLC25A36 | - | 38.10 | 9.76 | 25 | 1.04 |
| SLC12A6 | - | 14.47 | 6.26 | 25 | 0.83 |  | SLC25A37 | Bm | 823.72 | 515.08 | 25 | 1.56 |
| SLC12A7 | - | 2.93 | 1.88 | 25 | 0.55 |  | SLC25A38 | - | 37.15 | 13.55 | 25 | 1.02 |
| **SLC12A8** | **BTh** | **0.21** | **0.27** | **3** | **-** |  | SLC25A39 | - | 391.32 | 195.71 | 25 | 1.08 |
| SLC12A9 | - | 6.06 | 3.15 | 25 | 0.95 |  | SLC25A4 | HM | 18.26 | 6.68 | 25 | 1.44 |
| **SLC13A3** | **K** | **0.40** | **0.31** | **6** | **6.36** |  | SLC25A40 | - | 11.38 | 4.20 | 25 | 1.40 |
| **SLC13A5** | **L** | **0.15** | **0.19** | **7** | **0.48** |  | SLC25A42 | L | 4.60 | 1.84 | 25 | 0.95 |
| SLC14A1 | BPr | 7.49 | 5.43 | 25 | 1.76 |  | SLC25A43 | - | 8.60 | 2.86 | 25 | 1.25 |
| **SLC15A1** | **I** | **0.30** | **0.57** | **9** | **2.52** |  | SLC25A44 | - | 25.62 | 8.60 | 25 | 1.15 |
| SLC15A2 | PrBP | 0.62 | 0.50 | 21 | 0.65 |  | SLC25A45 | - | 6.60 | 2.80 | 25 | 0.97 |
| SLC15A3 | - | 17.00 | 4.69 | 25 | 0.64 |  | SLC25A46 | - | 31.25 | 8.50 | 25 | 0.91 |
| SLC15A4 | - | 8.55 | 3.77 | 25 | 0.67 |  | SLC25A47 | L | 0.53 | 0.51 | 13 | 0.73 |
| SLC16A1 | - | 9.49 | 5.34 | 25 | 1.26 |  | SLC25A5 | - | 467.78 | 105.64 | 25 | 1.16 |
| SLC16A10 | GiMSK | 0.79 | 1.31 | 13 | 0.57 |  | SLC25A51 | - | 12.74 | 4.07 | 25 | 1.23 |
| SLC16A11 | - | 0.54 | 0.36 | 23 | 0.74 |  | SLC25A52 | T | 41.85 | 24.02 | 25 | 1.33 |
| SLC16A13 | LK | 3.51 | 1.79 | 25 | 1.10 |  | SLC25A6 | - | 203.82 | 90.63 | 18 | 0.70 |
| SLC16A14 | - | 1.36 | 0.97 | 24 | 0.98 |  | SLC26A1 | KL | 0.03 | 0.00 | 3 | 1.09 |
| **SLC16A2** | **LB** | **0.15** | **0.15** | **14** | **0.37** |  | **SLC26A10** | **H** | **0.90** | **1.21** | **4** | **6.64** |
| SLC16A3 | MI | 17.75 | 6.44 | 25 | 1.19 |  | **SLC26A11** | **-** | **1.86** | **2.13** | **25** | **0.48** |
| SLC16A4 | K | 1.23 | 0.98 | 21 | 0.58 |  | SLC26A2 | I | 1.44 | 0.69 | 24 | 0.63 |
| SLC16A5 | - | 1.30 | 0.74 | 25 | 0.88 |  | SLC26A4 | Th | 0.35 | 0.49 | 6 | 1.36 |
| SLC16A6 | GiB | 5.60 | 3.34 | 25 | 1.60 |  | SLC26A5 | B | 0.43 | 0.40 | 7 | 1.53 |
| SLC16A9 | KA | 2.65 | 6.34 | 24 | 0.71 |  | **SLC26A6** | **-** | **2.71** | **2.47** | **25** | **2.22** |
| SLC17A1 | KL | 0.63 | 0.55 | 25 | 0.80 |  | SLC26A7 | Th | 1.05 | 0.99 | 19 | 0.84 |
| **SLC17A3** | **KL** | **0.17** | **0.25** | **10** | **-** |  | SLC26A8 | T | 1.77 | 2.09 | 25 | 0.95 |
| SLC17A5 | Th | 3.53 | 1.90 | 25 | 1.11 |  | SLC27A1 | - | 1.99 | 1.02 | 25 | 0.64 |
| **SLC17A7** | **B** | **0.34** | **0.21** | **9** | **3.14** |  | **SLC27A2** | **L** | **0.64** | **0.74** | **19** | **6.33** |
| SLC17A9 | L | 0.14 | 0.08 | 16 | 1.58 |  | SLC27A3 | - | 4.96 | 2.04 | 25 | 1.11 |
| **SLC18A2** | **BA** | **3.88** | **4.32** | **24** | **2.94** |  | SLC27A4 | I | 0.11 | 0.07 | 22 | 1.48 |
| SLC18A3 | B | 35.35 | 24.68 | 25 | 1.86 |  | SLC27A5 | L | 0.45 | 0.61 | 9 | 1.24 |
| SLC18B1 | - | 10.72 | 5.43 | 25 | 1.29 |  | SLC28A1 | IKL | 0.07 | 0.09 | 6 | 1.70 |
| SLC19A1 | LK | 1.20 | 0.62 | 25 | 1.14 |  | **SLC28A3** | **T** | **0.59** | **0.61** | **15** | **3.08** |
| SLC19A2 | M | 0.70 | 0.44 | 21 | 1.03 |  | SLC29A1 | - | 9.65 | 6.22 | 25 | 1.05 |
| SLC1A1 | IK | 0.89 | 0.83 | 15 | 0.63 |  | SLC29A2 | M | 0.43 | 0.35 | 15 | 0.92 |
| **SLC1A2** | **B** | **0.03** | **0.02** | **9** | **2.28** |  | SLC29A3 | - | 1.75 | 1.75 | 25 | 1.32 |
| SLC1A3 | B | 0.18 | 0.20 | 18 | 1.89 |  | SLC29A4 | Ad | 0.31 | 0.25 | 17 | 0.70 |
| SLC1A4 | - | 10.72 | 9.97 | 25 | 1.28 |  | SLC2A1 | S | 350.37 | 292.19 | 25 | 0.78 |
| SLC1A5 | - | 65.71 | 40.18 | 25 | 1.12 |  | **SLC2A10** | **L** | **0.42** | **0.80** | **17** | **3.53** |
| **SLC1A7** | **R** | **0.41** | **0.47** | **3** | **2.76** |  | SLC2A11 | - | 6.90 | 3.56 | 25 | 1.11 |
| SLC20A1 | - | 28.82 | 7.47 | 25 | 0.93 |  | SLC2A12 | R | 0.13 | 0.11 | 6 | 0.51 |
| SLC20A2 | Th | 2.34 | 1.56 | 24 | 0.83 |  | SLC2A13 | BTh | 0.98 | 1.40 | 19 | 0.91 |
| SLC22A1 | L | 0.35 | 0.29 | 18 | 1.51 |  | SLC2A3 | Bm | 41.15 | 34.97 | 19 | 1.24 |
| SLC22A15 | BBm | 1.84 | 1.83 | 25 | 1.10 |  | **SLC2A4** | **HM** | **1.67** | **1.52** | **25** | **0.45** |
| SLC22A16 | BmThT | 2.88 | 2.05 | 24 | 0.86 |  | **SLC2A5** | **BmI** | **12.12** | **14.45** | **25** | **4.14** |
| SLC22A17 | B | 0.96 | 1.58 | 21 | 1.40 |  | SLC2A6 | BBmP | 5.38 | 2.57 | 25 | 1.09 |
| SLC22A18 | ILK | 0.05 | 0.04 | 15 | 1.26 |  | SLC2A7 | I | 0.14 | 0.20 | 3 | 1.32 |
| SLC22A23 | - | 6.14 | 5.06 | 25 | 1.03 |  | SLC2A9 | KL | 0.69 | 0.38 | 24 | 0.86 |
| **SLC22A25** | **L** | **1.30** | **3.18** | **7** | **18.26** |  | SLC30A1 | L | 12.62 | 6.50 | 25 | 1.09 |
| **SLC22A3** | **LM** | **0.69** | **0.87** | **5** | **2.34** |  | **SLC30A10** | **L** | **0.69** | **1.18** | **4** | **13.34** |
| **SLC22A31** | **BP** | **0.23** | **0.48** | **16** | **2.81** |  | **SLC30A3** | **BT** | **0.39** | **0.37** | **5** | **2.72** |
| SLC22A4 | - | 4.63 | 3.53 | 25 | 1.03 |  | **SLC30A4** | **Pr** | **1.03** | **0.75** | **25** | **0.38** |
| SLC22A5 | KM | 0.75 | 0.61 | 18 | 1.55 |  | SLC30A5 | - | 4.43 | 3.07 | 25 | 0.68 |

**Table S6.** Continued.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene name** | **Tissue***a* | **Mean (RPM)***b* | **SD***b* | **n***b* | **FC***c* |  | **Gene name** | **Tissue***a* | **Mean (RPM)***b* | **SD** *b* | **n***b* | **FC***c* |
| **SLC30A6** | **-** | **0.24** | **0.20** | **15** | **0.48** |  | SLC4A3 | HO | 0.84 | 0.84 | 17 | 0.75 |
| SLC30A7 | - | 24.05 | 11.07 | 25 | 1.09 |  | SLC4A4 | K | 1.03 | 0.95 | 23 | 1.10 |
| SLC30A9 | - | 32.45 | 10.89 | 25 | 1.02 |  | **SLC4A5** | **R** | **0.27** | **0.23** | **21** | **0.40** |
| SLC31A1 | LIK | 7.06 | 2.67 | 25 | 1.26 |  | SLC4A7 | I | 8.33 | 4.74 | 25 | 1.66 |
| SLC31A2 | - | 0.96 | 0.69 | 23 | 1.51 |  | SLC4A8 | BT | 1.26 | 1.22 | 18 | 1.46 |
| SLC33A1 | - | 17.40 | 8.28 | 25 | 1.14 |  | SLC4A9 | K | 1.73 | 1.73 | 25 | 1.48 |
| SLC34A1 | K | 0.42 | 0.32 | 21 | 1.46 |  | SLC50A1 | - | 47.22 | 25.39 | 25 | 1.56 |
| **SLC34A2** | **PT** | **0.21** | **0.23** | **4** | **10.64** |  | **SLC51A** | **IL** | **0.41** | **0.72** | **11** | **4.25** |
| SLC35A1 | - | 7.42 | 4.03 | 25 | 1.56 |  | SLC51B | I | 0.18 | 0.27 | 5 | 0.89 |
| SLC35A2 | - | 1.49 | 0.88 | 24 | 1.04 |  | **SLC52A1** | **I** | **0.08** | **0.08** | **17** | **0.21** |
| SLC35A4 | - | 71.93 | 16.32 | 25 | 0.75 |  | SLC52A2 | - | 4.08 | 2.19 | 25 | 0.76 |
| SLC35A5 | - | 23.87 | 14.42 | 25 | 0.65 |  | **SLC52A3** | **T** | **1.07** | **1.32** | **14** | **2.48** |
| SLC35B1 | - | 13.12 | 8.30 | 25 | 1.62 |  | SLC5A1 | I | 0.31 | 0.49 | 7 | 1.73 |
| SLC35B2 | - | 0.66 | 0.44 | 24 | 0.50 |  | **SLC5A10** | **K** | **0.40** | **0.29** | **15** | **2.98** |
| SLC35B3 | - | 5.85 | 2.72 | 25 | 1.15 |  | **SLC5A11** | **BI** | **0.21** | **0.29** | **5** | **0.37** |
| SLC35B4 | - | 4.14 | 2.80 | 25 | 1.33 |  | SLC5A12 | IK | 0.58 | 0.74 | 4 | 0.79 |
| SLC35C1 | L | 5.26 | 2.19 | 25 | 0.86 |  | SLC5A3 | K | 1.19 | 0.77 | 24 | 1.08 |
| SLC35C2 | - | 36.46 | 12.00 | 25 | 1.59 |  | SLC5A4 | I | 0.90 | 1.17 | 20 | 0.78 |
| SLC35D1 | L | 2.85 | 1.80 | 25 | 1.03 |  | **SLC5A6** | **L** | **9.60** | **5.73** | **24** | **2.36** |
| **SLC35D2** | **-** | **4.35** | **3.15** | **25** | **0.43** |  | **SLC5A9** | **I** | **0.41** | **0.36** | **8** | **2.72** |
| **SLC35D3** | **BR** | **0.03** | **0.01** | **4** | **2.56** |  | SLC6A1 | BL | 0.21 | 0.28 | 7 | 1.01 |
| SLC35E1 | - | 19.58 | 7.45 | 25 | 1.21 |  | **SLC6A11** | **BS** | **0.89** | **2.29** | **7** | **16.43** |
| SLC35E2 | - | 24.84 | 10.30 | 25 | 1.01 |  | **SLC6A13** | **KR** | **0.25** | **0.57** | **9** | **0.13** |
| SLC35E3 | - | 2.61 | 2.16 | 24 | 1.16 |  | **SLC6A15** | **B** | **0.28** | **0.12** | **4** | **-** |
| SLC35E4 | MT | 0.37 | 0.43 | 22 | 0.94 |  | SLC6A16 | T | 1.34 | 1.20 | 23 | 1.53 |
| **SLC35F1** | **B** | **0.17** | **0.18** | **5** | **-** |  | **SLC6A17** | **B** | **0.05** | **0.06** | **5** | **-** |
| SLC35F2 | - | 0.33 | 0.27 | 24 | 1.40 |  | **SLC6A19** | **I** | **3.77** | **6.74** | **23** | **3.97** |
| SLC35F3 | B | 0.79 | 0.72 | 10 | 1.41 |  | **SLC6A20** | **IR** | **0.10** | **0.21** | **10** | **0.29** |
| SLC35F5 | - | 15.09 | 6.06 | 25 | 1.01 |  | **SLC6A4** | **IP** | **1.87** | **1.99** | **24** | **2.01** |
| SLC35G1 | IR | 0.31 | 0.25 | 10 | 0.77 |  | SLC6A6 | R | 33.33 | 12.91 | 25 | 1.51 |
| **SLC35G2** | **-** | **0.17** | **0.13** | **12** | **5.46** |  | SLC6A8 | - | 49.20 | 34.39 | 25 | 1.30 |
| SLC35G3 | MT | 71.39 | 37.78 | 25 | 1.60 |  | SLC6A9 | BS | 1.02 | 1.26 | 12 | 0.83 |
| SLC35G5 | T | 63.84 | 38.36 | 25 | 1.43 |  | **SLC7A1** | **B** | **27.19** | **17.95** | **25** | **2.25** |
| SLC36A1 | B | 2.16 | 1.57 | 25 | 0.50 |  | **SLC7A10** | **BBr** | **0.03** | **0.02** | **9** | **0.49** |
| **SLC36A3** | **T** | **0.03** | **0.01** | **4** | **-** |  | SLC7A11 | B | 0.64 | 0.58 | 22 | 0.57 |
| SLC36A4 | - | 8.73 | 4.15 | 25 | 0.85 |  | **SLC7A2** | **LThM** | **0.34** | **0.45** | **12** | **4.75** |
| SLC37A2 | - | 1.61 | 1.02 | 24 | 0.57 |  | SLC7A5 | Bm | 47.20 | 37.84 | 25 | 0.96 |
| SLC37A3 | - | 3.55 | 2.93 | 24 | 1.20 |  | SLC7A6 | M | 3.45 | 2.10 | 25 | 0.66 |
| SLC38A1 | - | 3.35 | 1.48 | 25 | 0.56 |  | SLC7A6OS | - | 28.14 | 7.33 | 25 | 1.13 |
| SLC38A10 | - | 3.42 | 1.38 | 25 | 0.60 |  | SLC7A7 | IK | 18.75 | 6.94 | 25 | 0.51 |
| SLC38A11 | KPrGi | 1.03 | 0.84 | 21 | 0.52 |  | SLC7A8 | Th | 0.83 | 0.89 | 24 | 0.61 |
| SLC38A2 | - | 36.86 | 13.20 | 25 | 1.34 |  | **SLC7A9** | **IK** | **0.32** | **0.48** | **5** | **6.20** |
| **SLC38A3** | **L** | **0.43** | **0.71** | **16** | **3.37** |  | **SLC8A1** | **H** | **0.83** | **0.61** | **4** | **3.17** |
| **SLC38A4** | **L** | **0.71** | **1.03** | **13** | **4.29** |  | **SLC8A3** | **BM** | **1.22** | **1.60** | **19** | **2.79** |
| SLC38A5 | BmGi | 4.84 | 2.88 | 25 | 0.70 |  | SLC9A1 | - | 9.07 | 6.05 | 25 | 1.31 |
| SLC38A6 | - | 3.47 | 2.33 | 24 | 0.73 |  | SLC9A3 | IK | 0.14 | 0.11 | 4 | 0.84 |
| SLC38A7 | - | 0.93 | 1.39 | 24 | 1.33 |  | **SLC9A5** | **B** | **0.93** | **0.74** | **9** | **3.92** |
| SLC38A9 | T | 1.72 | 1.68 | 25 | 1.10 |  | SLC9A6 | B | 2.01 | 1.43 | 24 | 0.92 |
| SLC39A1 | - | 11.06 | 3.08 | 25 | 0.75 |  | SLC9A7 | B | 18.83 | 11.21 | 25 | 1.11 |
| SLC39A10 | BTh | 0.59 | 0.53 | 12 | 1.77 |  | SLC9A8 | - | 11.23 | 5.65 | 25 | 0.67 |
| SLC39A11 | - | 0.67 | 0.55 | 24 | 0.72 |  | SLC9A9 | - | 11.01 | 7.68 | 25 | 1.48 |
| SLC39A13 | -  | 2.16 | 0.88 | 25 | 0.59 |  | SLC9B1 | T | 0.82 | 0.66 | 21 | 1.18 |
| SLC39A14 | LI | 0.35 | 0.29 | 21 | 1.11 |  | SLC9B2 | L | 3.55 | 2.02 | 25 | 0.56 |
| **SLC39A2** | **PrS** | **0.02** | **0.01** | **4** | **0.37** |  | **SLC9C1** | **T** | **0.76** | **0.69** | **21** | **2.55** |
| SLC39A3 | - | 11.28 | 6.95 | 25 | 1.06 |  | SLCO1A2 | BLR | 0.59 | 0.63 | 19 | 0.98 |
| SLC39A4 | I | 15.43 | 4.94 | 25 | 1.25 |  | SLCO1B1 | L | 0.41 | 0.29 | 7 | 1.82 |
| SLC39A5 | IKL | 0.67 | 0.72 | 22 | 1.61 |  | SLCO1B3 | L | 0.07 | 0.05 | 5 | 1.83 |
| **SLC39A6** | **P** | **0.17** | **0.13** | **24** | **0.49** |  | **SLCO1B7** | **Br** | **0.25** | **0.26** | **3** | **2.37** |
| SLC39A7 | - | 1.11 | 0.49 | 18 | 0.77 |  | **SLCO1C1** | **BR** | **0.06** | **0.06** | **4** | **-** |
| SLC39A8 | - | 72.09 | 27.47 | 25 | 1.06 |  | SLCO2A1 | PTh | 7.67 | 5.96 | 25 | 1.13 |
| SLC39A9 |  | 17.43 | 5.78 | 25 | 1.16 |  | SLCO2B1 | LPI | 1.85 | 1.45 | 24 | 1.79 |
| SLC3A1 | IK | 0.16 | 0.18 | 6 | 0.55 |  | SLCO3A1 | - | 8.79 | 3.34 | 25 | 1.48 |
| SLC3A2 | - | 13.70 | 4.76 | 25 | 1.28 |  | SLCO4A1 | - | 3.15 | 2.33 | 25 | 1.80 |
| SLC40A1 | - | 186.66 | 106.67 | 25 | 1.44 |  | SLCO4C1 | K | 6.80 | 3.09 | 25 | 1.53 |
| SLC41A1 | HT | 7.65 | 2.93 | 25 | 0.75 |  | **SLCO5A1** | **HM** | **0.71** | **0.68** | **17** | **2.15** |
| SLC41A2 | LI | 2.26 | 2.39 | 25 | 0.80 |  | FCGRT | - | 9.03 | 3.12 | 25 | 0.68 |
| SLC41A3 | - | 15.02 | 4.88 | 25 | 1.00 |  | **B2M** | **-** | **4641.13** | **2969.00** | **25** | **2.26** |
| SLC43A1 | - | 2.97 | 3.06 | 25 | 0.74 |  |   |  |  |  |  |   |
| SLC43A2 | K | 5.45 | 1.88 | 25 | 0.70 |  |   |  |  |  |  |   |
| SLC43A3 | LTh | 10.26 | 4.54 | 25 | 1.23 |  |   |  |  |  |  |   |
| SLC44A1 | B | 11.11 | 10.57 | 25 | 1.80 |  |   |  |  |  |  |   |
| SLC44A2 | - | 31.02 | 19.63 | 25 | 1.41 |  |   |  |  |  |  |   |
| **SLC44A3** | **-** | **0.15** | **0.13** | **6** | **3.84** |  |   |  |  |  |  |   |
| SLC44A4 | I | 0.13 | 0.07 | 5 | 1.17 |  |   |  |  |  |  |   |
| SLC44A5 | T | 0.36 | 0.46 | 9 | 1.94 |  |   |  |  |  |  |   |
| SLC45A1 | B | 0.52 | 0.40 | 18 | 1.50 |  |   |  |  |  |  |   |
| SLC45A3 | Pr | 0.79 | 0.46 | 25 | 0.52 |  |   |  |  |  |  |   |
| SLC45A4 | - | 3.08 | 1.80 | 25 | 1.42 |  |   |  |  |  |  |   |
| SLC46A1 | I | 0.82 | 0.83 | 19 | 1.12 |  |   |  |  |  |  |   |
| SLC46A2 | SP | 2.69 | 3.91 | 24 | 0.59 |  |   |  |  |  |  |   |
| SLC46A3 | IL | 2.92 | 1.93 | 25 | 0.74 |  |   |  |  |  |  |   |
| SLC47A1 | ALK | 0.59 | 0.79 | 18 | 1.77 |  |   |  |  |  |  |   |
| SLC48A1 | B | 12.74 | 7.85 | 25 | 1.22 |  |   |  |  |  |  |   |
| SLC4A1 | Bm | 485.17 | 337.47 | 25 | 1.06 |  |   |  |  |  |  |   |
| **SLC4A11** | **Th** | **0.59** | **0.65** | **18** | **2.31** |  |   |  |  |  |  |   |
| SLC4A2 | LR | 6.95 | 2.38 | 25 | 0.87 |  |   |  |  |  |  |   |

*a*Tissue enrichment data from the Human Protein Atlas and NCBI Gene databases: L, liver; I, intestine, K, kidney; Gi, gastrointestinal; P, lung; B, brain; A, adrenal gland; Ad, adipose; S, skin; T, testes; Pr, prostate; Br, breast; M, muscle; H, heart; Th, thyroid; Bm, bone marrow; R, retina; O, ovary; U, uterus; -, ubiquitous/no enrichment. Tissue enrichment is listed in the order of most to least enriched. *b* Mean (and SD) of expression levels (RPM) in CVD plasma samples (*n* = 25). *c* Fold change (FC) relative to healthy samples (*n* = 7), bold font denotes disease-related differential expression (lower than 0.5 or higher than 2 fold) and - symbols mean not detected in the healthy set. *d* Expression data of selected targets (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP3A7 and ABCB1) were vetted, normalized to liver-specific shedding and correlated with activity phenotype.

**Table S7.** Liquid biopsy expression of pharmacodynamic drug targets of medications received by the CVD cohort for the management of cardiovascular and related diseases. The total number of patients was 30, whereas the number of samples, which passed QC, was 25.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug classes/drugs** | **No. of patients** | **Drug target (nature of interaction)** | **Targeted tissue/cell type (expression site)** | **Gene name** | **Expression in liquid biopsy (CVD)** | **FC** *f* |
| **Mean±SD (%CV)** | **Range (*n*)** |  |
| Lipid lowering drugs: statins (atorvastatin, rosuvastatin, pravastatin, simvastatin) | 17 | 3-Hydroxymethylglutaryl-coenzyme A, HMG-CoA, reductase (inhibitor) | Liver (ubiquitous expression) | HMGCR | 6.30±3.09 (49%) | 1.80‒16.86 (25) | 1.14 |
| Cardio-selective beta blockers (metoprolol, bisoprolol) | 17 | Beta-1 adrenergic receptor (inhibitor) | Heart (specific to heart tissue) | ADRB1 | 41.35±23.76 (57%) | 9.13‒113.72 (25) | 1.11 |
| Heparins (heparin, enoxaparin, fondaparinux) | 18 | Antithrombin (potentiator, leading to inhibition of coagulation factor Xa and thrombin)*a* | Blood (expressed in liver) | SERPINC1 | 0.38±0.23 (61%) | 0.12‒1.11 (14) | 1.27 |
| Antithrombotic agents (apixaban, rivaroxaban) | 16 | Coagulation factor Xa (inhibitor) | Blood (expressed in liver) | F10 | 0.34±0.24 (71%) | 0.12‒0.72 (8) | 1.07 |
| Antiplatelet agents (ticagrelor, clopidogrel, prasugrel)  | 14 | P2Y purinoceptor 12 (inhibitor) | Platelets (expressed in brain and other organs) | P2RY12 | 30.80±23.74 (77%) | 5.05‒113.34 (25) | 1.03 |
| Antiplatelet agent (acetyl salicylic acid/Aspirin) | 16 | Platelet cyclooxygenase 1 (inhibitor of thromboxane A2 formation) | Platelets (ubiquitous expression) | PTGS1 | 126.85±139.88 (110%) | 10.32‒674.44 (25) | **2.06** |
| Angiotensin converting enzyme, ACE, inhibitors (enalapril, perindopril, lisinopril) | 12 | Angiotensin converting enzyme, ACE (inhibitor) | Lungs, kidneys (ubiquitous expression) | ACE | 3.13±1.89 (60%) | 0.04‒6.71 (25) | 0.72 |
| Angiotensin receptor blockers (valsartan, telmisartan, irbesartan, losartan, olemsartan) | 10 | Angiotensin II receptor type 1, AT1 (inhibitor) | Blood vessels (ubiquitous expression) | AGTR1 | 0.09±0.05 (57%) | 0.05‒0.12 (2) | - |
| Calcium channel blockers (amlodipine) | 6 | Voltage-dependent L-type calcium channel, subunit alpha-1C (inhibitor) | Blood vessels (ubiquitous expression) | CACNA1C | 0.42±0.28 (67%) | 0.18‒0.73 (3) | **4.34** |
| Moxonidine | 1 | Imidazoline receptor subtype 1 (agonist) | Rostral ventrolateral medulla oblongata (ubiquitous expression) | NISCH | 12.53±3.18 (25%) | 5.08‒18.83 (25) | 0.76 |
| Vasodilators (isosorbide dinitrate, nitroglycerine) | 3 | Guanylyl cyclase (agonist) | Blood vessels (ubiquitous expression) | GUCY1A1 *b*/1B1 *c* | 18.22±10.71 (59%) *b*; 42.82±40.18 (94%) *c* | 6.65‒49.04 (25) *b*; 7.59‒191.46 (25) *c* | 1.79 *b*; **2.77** *c* |
| Amiodarone | 1 | hERG-encoded K+ channel (inhibitor) | Heart (ubiquitous expression) | KCNH2 | 0.76±0.65 (85%) | 0.03‒2.48 (22) | 0.95 |
| Eplerenone, spironolactone | 5 | Mineralocorticoid receptor (inhibitor) | Epithelial, e.g., kidney, and non-epithelial, e.g., heart and blood vessels, receptors (Ubiquitous expression) | NR3C2 | 42.02±23.20 (55%) | 8.09‒89.17 (25) | 0.65 |
| Lipid lowering drug (ezetimibe) | 1 | Niemann-Pick C1-Like 1 (NPC1L1) protein (inhibitor) | Intestinal and hepatobiliary tissue (expressed in GI tract and liver) | NPC1L1 | 0.47 | 0.47‒0.47 (1) | **2.30** |
| Digoxin | 1 | Myocardial Na-K ATPase (inhibitor) | Heart (expressed ubiquitously) | ATP1A1 | 97.30±21.70 (22%) | 58.87‒128.06 (25) | 0.88 |
| Insulin | 5 | Insulin receptor (agonist) | Liver, muscle and adipose tissue (ubiquitous expression) | INSR | 5.46±3.99 (73%) | 0.85‒15.51 (25) | 1.31 |
| Metformin | 4 | Mitochondrial complex I, ND3 core subunit, and mitochondrial glycerol-3-phosphate dehydrogenase (inhibitor) | Liver, intestine | MT-ND3*d*, GPD2*e* | -*d*; 33.42±12.57 (38%) *e* | -*d*; 13.20‒67.39 (25) *e* | -*d*; 1.81 *e* |
| Antidiabetics: DPP4 inhibitors (sitagliptin) | 2 | Dipeptide peptidase 4 (inhibitor) | Intestine (ubiquitous expression) | DPP4 | 6.02±3.11 (52%) | 1.01‒13.89 (25) | 0.66 |
| Antidiabetics: incretin mimetics (duaglutide, liraglutide) | 2 | Glucagon-like peptide 1 receptor (agonist) | Pancreas (specific expression) | GLP1R | 0.28±0.23 (83%) | 0.07‒0.52 (3) | 1.29 |

*a*Enoxaparin primarily inhibits factor Xa and to a lesser extent thrombin while fondaparinux inhibits factor Xa selectively; *b* expression levels of GUCY1A1; *c* expression levels of GUCY1B1; *d*TM-ND3 is encoded by mitochondrial DNA; *e* expression levels of GPD2; *f* fold change (FC) relative to healthy samples (*n* = 7), bold font denotes differential expression.



**Figure S1.** (a)Workflow ofliquid biopsy technology and (b) assessment of liquid biopsy measurements in all replicates (*n* = 92) of the CVD samples. A total of 40 replicates failed quality control (QC) at the cDNA or sequencing stage, while several measurements were below the limit of quantification (BLQ) in the case of CYP enzymes. Liver-specific shedding was measured in all replicates that passed QC (*n* = 52). Abbreviations: BLQ, below the limit of quantification; cDNA, complementary DNA; cfRNA, cell-free RNA; CYP, cytochrome P450; QC, quality control.



**Figure S2.** Concept and determination of exosomal shedding from liver into the bloodstream. (a) The liver sheds exosomes continuously into the blood; exosomes contain RNA of enzymes/transporters and liver-specific markers. (b) Exosomes isolated and visualized by scanning electron microscopy (magnification: 11,000X) are generally 30-100 nm in size. (c) The level of liver shedding is determined using a combination of liver-specific markers measured in isolated plasma exosomes (list of 13 markers). Shedding was significantly higher and more variable in *liver cancer* and *CVD* than in healthy donors (pairwise *t*-test). The whiskers represent the range, the boxes are the 25th and 75th percentiles, the lines are the medians and the + signs are the means. In parentheses is the maximum-to-minimum fold difference in shedding in each cohort. Abbreviations: CV, coefficient of variation; CVD, cardiovascular disease; RPM, reads per million.



**Figure S3.** Covariates of shedding in the CVD cohort. Shedding levels in (a) males and females, (b) different age groups, (c) BMI groups, (d) smokers/non-smokers and drinkers/non-drinkers are presented. Differences were assessed using ANOVA (BMI) or *t*-test (sex, age, smoking/drinking) with Welch’s correction; \* *p* < 0.05. BMI classification (US CDC): BMI < 18.5 kg/m2, underweight range; BMI 18.5-24.9 kg/m2, healthy weight range; BMI 25.0-29.9 kg/m2, overweight range; BMI 30.0 kg/m2 or higher, obese range. Abbreviations: BMI, body mass index; RPM, reads per million.



**Figure S4.** Correlation between concentration (ratio) and AUC (ratio) data measured using the Geneva cocktail. Metabolic ratios and AUC ratios were measured for CYP substrates (caffeine for CYP1A2, bupropion for CYP2B6, flurbiprofen for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6, and midazolam for CYP3A). Concentration and AUC of fexofenadine were used to assess activity of P-gp.



**Figure S5.** Correlation between liquid biopsy replicate measurements and activity phenotype of CVD patient samples. The assessment was based on quantification of the RNA expression of CYP enzymes and ABCB1 in plasma-derived exosomes and activity measurements of the corresponding proteins (CYP enzymes and P-gp) in dried blood spots against the Geneva cocktail. Activity was measured as metabolic ratios (for CYPs) and concentration of fexofenadine (for P-gp) at 2 h post administration. The dashed box (in the case of CYP2B6 correlation) encloses outlier readouts. Abbreviations: LB, liquid biopsy; MR, metabolic ratio; RPM, reads per million.