

Supporting Information

Metabolic profile of male cannabis users and estimation of candidate biomarkers

Esin Oz¹, Merve Kasikci², İbrahim Celik³, Mukaddes Gurler^{1,4*}

¹Department of Medical Biochemistry, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

²Department of Biostatistics, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

³ Faculty of Medicine, Hacettepe University, Ankara, Türkiye

⁴Department of Medical Biochemistry and Forensic Medicine, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

* Corresponding Author

Supporting Information – Table of Contents

- 1. P-values, fold change values, and regulation status for statistically significant metabolites in cannabis users compared to non-users** **Page S3-S6**
- 2. VIP scores of metabolites** **Page S7-S8**
- 3. Results of pathway enrichment analysis conducted on MetaboAnalyst based on the KEGG database** **Page S9**
- 4. Results of pathway enrichment analysis conducted on CPDB based on multiple databases** **Page S10-S11**

P-values, fold change values, and regulation status for statistically significant metabolites are presented in Table S1. Out of over 200 metabolites detected in cannabis user samples, 92 with p-values < 0.05 were identified for further analysis, including 38 that decreased and 54 that increased compared to non-users.

Table S1. Results for metabolites that differed significantly between groups.

| No | KEGG ID | KEGG Link | Name | p.value | FDR | Fold Change | UP/DOWN |
|----|---------|---|---|---------|--------|-------------|---------|
| 1 | C09640 | https://www.genome.jp/entry/C09640 | (-)-Salsoline | <0.001 | <0.001 | 6.288 | UP |
| 2 | C16613 | https://www.genome.jp/entry/C16613 | 6-Thiourate | <0.001 | <0.001 | 8.666 | UP |
| 3 | C01211 | https://www.genome.jp/entry/C01211 | Procollagen 5-hydroxy-L-lysine | <0.001 | <0.001 | 32.194 | UP |
| 4 | C00120 | https://www.genome.jp/entry/C00120 | Biotin | <0.001 | 0.001 | 3.165 | DOWN |
| 5 | C03087 | https://www.genome.jp/entry/C03087 | 5-Acetamidovalerate | <0.001 | <0.001 | 23.151 | UP |
| 6 | C01449 | https://www.genome.jp/entry/C01449 | Queueine | <0.001 | <0.001 | 2.404 | DOWN |
| 7 | C05933 | https://www.genome.jp/entry/C05933 | N(omega)-Hydroxyarginine | <0.001 | 0.002 | 3.115 | DOWN |
| 8 | C05401 | https://www.genome.jp/entry/C05401 | Galactosylglycerol | <0.001 | <0.001 | 2.075 | DOWN |
| 9 | C00670 | https://www.genome.jp/entry/C00670 | Glycerophosphocholine | <0.001 | 0.001 | 7.042 | DOWN |
| 10 | C01595 | https://www.genome.jp/entry/C01595 | Linoleic acid | <0.001 | <0.001 | 3.788 | DOWN |
| 11 | C00957 | https://www.genome.jp/entry/C00957 | 3-Mercaptopyruvic acid | <0.001 | <0.001 | 5.714 | DOWN |
| 12 | C02218 | https://www.genome.jp/entry/C02218 | 2-Aminoacrylic acid | <0.001 | <0.001 | 6.828 | UP |
| 13 | C02576 | https://www.genome.jp/entry/C02576 | Perillyl aldehyde | <0.001 | <0.001 | 6.024 | DOWN |
| 14 | C08012 | https://www.genome.jp/entry/C08012 | Levomethadyl Acetate | <0.001 | <0.001 | 6.757 | DOWN |
| 15 | C00093 | https://www.genome.jp/entry/C00093 | Glycerol 3-phosphate | <0.001 | <0.001 | 3.861 | DOWN |
| 16 | C00664 | https://www.genome.jp/entry/C00664 | 5-Formiminotetrahydrofollic acid | <0.001 | <0.001 | 5.859 | UP |
| 17 | C05823 | https://www.genome.jp/entry/C05823 | 3-Mercaptolactic acid | <0.001 | <0.001 | 4.721 | UP |
| 18 | C04441 | https://www.genome.jp/entry/C04441 | 2-(3-Carboxy-3-aminopropyl)-L-histidine | <0.001 | 0.001 | 1.953 | DOWN |
| 19 | C00086 | https://www.genome.jp/entry/C00086 | Urea | <0.001 | <0.001 | 9.091 | DOWN |
| 20 | C00390 | https://www.genome.jp/entry/C00390 | QH2 | <0.001 | 0.001 | 2.532 | DOWN |
| 21 | C00850 | https://www.genome.jp/entry/C00850 | Aryl sulfate; Phenol sulfate | <0.001 | <0.001 | 3.817 | DOWN |
| 22 | C03033 | https://www.genome.jp/entry/C03033 | 3-Methoxy-4-hydroxyphenylglycol glucuronide | <0.001 | <0.001 | 2.584 | DOWN |
| 23 | C01031 | https://www.genome.jp/entry/C01031 | S-Formylglutathione | <0.001 | <0.001 | 7.213 | UP |
| 24 | C03406 | https://www.genome.jp/entry/C03406 | Argininosuccinic acid | <0.001 | <0.001 | 3.247 | DOWN |
| 25 | C06423 | https://www.genome.jp/entry/C06423 | Caprylic acid | <0.001 | <0.001 | 5.952 | DOWN |

| | | | | | | | |
|----|--------|---|---|--------|--------|--------|------|
| 26 | C02325 | https://www.genome.jp/entry/C02325 | Sinapyl alcohol | <0.001 | <0.001 | 7.663 | UP |
| 27 | C01152 | https://www.genome.jp/entry/C01152 | 1-Methylhistidine | <0.001 | 0.001 | 7.246 | DOWN |
| 28 | C07535 | https://www.genome.jp/entry/C07535 | Benzo[a]pyrene | <0.001 | 0.001 | 2.688 | DOWN |
| 29 | C16014 | https://www.genome.jp/entry/C16014 | cis-stilbene oxide | <0.001 | <0.001 | 3.399 | UP |
| 30 | C05504 | https://www.genome.jp/entry/C05504 | Estriol-16-Glucuronide | 0.001 | 0.003 | 2.77 | DOWN |
| 31 | C00037 | https://www.genome.jp/entry/C00037 | Glycine | <0.001 | <0.001 | 3.8 | UP |
| 32 | C00245 | https://www.genome.jp/entry/C00245 | Taurine | <0.001 | <0.001 | 3.323 | UP |
| 33 | C00864 | https://www.genome.jp/entry/C00864 | Pantothenic acid | <0.001 | <0.001 | 2.41 | UP |
| 34 | C05552 | https://www.genome.jp/entry/C05552 | Bioceytin | <0.001 | <0.001 | 5.917 | DOWN |
| 35 | C00353 | https://www.genome.jp/entry/C00353 | Geranylgeranyl-PP | <0.001 | 0.001 | 3.968 | DOWN |
| 36 | C05839 | https://www.genome.jp/entry/C05839 | cis-beta-D-Glucosyl-2-hydroxycinnamate | <0.001 | <0.001 | 4.371 | UP |
| 37 | C16015 | https://www.genome.jp/entry/C16015 | (+)-(1R,2R)-1,2-Diphenylethane-1,2-diol | <0.001 | 0.001 | 2.237 | DOWN |
| 38 | C05985 | https://www.genome.jp/entry/C05985 | 2-Propyn-1-al | <0.001 | <0.001 | 4.717 | DOWN |
| 39 | C05588 | https://www.genome.jp/entry/C05588 | Metanephrine | 0.005 | 0.014 | 1.661 | DOWN |
| 40 | C14852 | https://www.genome.jp/entry/C14852 | Benzo[a]pyrene-7,8-diol | 0.006 | 0.015 | 2.427 | DOWN |
| 41 | C02727 | https://www.genome.jp/entry/C02727 | N6-Acetyl-L-lysine | 0.002 | 0.006 | 3.077 | DOWN |
| 42 | C00409 | https://www.genome.jp/entry/C00409 | Methanethiol | <0.001 | <0.001 | 3.861 | DOWN |
| 43 | C03492 | https://www.genome.jp/entry/C03492 | D-4'-Phosphopantothenate | <0.001 | 0.001 | 2.173 | UP |
| 44 | C06755 | https://www.genome.jp/entry/C06755 | Chloroacetic acid | <0.001 | <0.001 | 4.454 | UP |
| 45 | C00988 | https://www.genome.jp/entry/C00988 | Phosphoglycolic acid | <0.001 | 0.002 | 13.158 | DOWN |
| 46 | C16632 | https://www.genome.jp/entry/C16632 | alpha-Fluoro-beta-alanine | <0.001 | <0.001 | 8.599 | UP |
| 47 | C03078 | https://www.genome.jp/entry/C03078 | 4-Guanidinobutanamide | <0.001 | <0.001 | 3.708 | UP |
| 48 | C01119 | https://www.genome.jp/entry/C01119 | Oxidized dithiothreitol | 0.001 | 0.004 | 6.41 | DOWN |
| 49 | C00327 | https://www.genome.jp/entry/C00327 | Citrulline | <0.001 | 0.001 | 6.095 | UP |
| 50 | C03413 | https://www.genome.jp/entry/C03413 | N1,N12-Diacetylspermine | 0.028 | 0.054 | 3.002 | DOWN |
| 51 | C00058 | https://www.genome.jp/entry/C00058 | Formic acid | <0.001 | <0.001 | 3.096 | DOWN |
| 52 | C02373 | https://www.genome.jp/entry/C02373 | 3a,7b,12a-Trihydroxy-5a-Cholanoic acid | <0.001 | 0.002 | 2.294 | DOWN |
| 53 | C03340 | https://www.genome.jp/entry/C03340 | L-2,3-Dihydrodipicolinate | <0.001 | <0.001 | 2.432 | UP |
| 54 | C08261 | https://www.genome.jp/entry/C08261 | Azelaic acid | <0.001 | 0.001 | 3.831 | DOWN |
| 55 | C00440 | https://www.genome.jp/entry/C00440 | 5-Methyltetrahydrofolic acid | 0.016 | 0.034 | 1.65 | DOWN |
| 56 | C16662 | https://www.genome.jp/entry/C16662 | L-alpha-Acetyl-N,N-dinormethadol | 0.014 | 0.030 | 4.098 | DOWN |

| | | | | | | | |
|----|--------|---|--|--------|--------|-------|------|
| 57 | C04352 | https://www.genome.jp/entry/C04352 | 4'-Phosphopantothenoylcysteine | <0.001 | 0.001 | 2.159 | UP |
| 58 | C06350 | https://www.genome.jp/entry/C06350 | Tetrahydropapaveroline; (R,S)-Norlaudanoline; Norlaudanoline | 0.027 | 0.052 | 2.762 | DOWN |
| 59 | C00621 | https://www.genome.jp/entry/C00621 | Dolichyl diphosphate | <0.001 | 0.001 | 2.042 | UP |
| 60 | C15650 | https://www.genome.jp/entry/C15650 | 5-(Methylthio)-2,3-dioxopentyl phosphate | 0.001 | 0.002 | 2.363 | UP |
| 61 | C03356 | https://www.genome.jp/entry/C03356 | 3-Phospho-D-erythronate | <0.001 | <0.001 | 2.52 | UP |
| 62 | C00073 | https://www.genome.jp/entry/C00073 | L-Methionine | 0.047 | 0.081 | 1.506 | DOWN |
| 63 | C01620 | https://www.genome.jp/entry/C01620 | Threonic acid | <0.001 | <0.001 | 2.154 | UP |
| 64 | C02637 | https://www.genome.jp/entry/C02637 | 3-Dehydroshikimate | <0.001 | 0.001 | 2.212 | UP |
| 65 | C06206 | https://www.genome.jp/entry/C06206 | Benzoyl phosphate | 0.002 | 0.006 | 2.428 | UP |
| 66 | C14873 | https://www.genome.jp/entry/C14873 | Thiodiacetic acid sulfoxide | 0.004 | 0.010 | 1.861 | UP |
| 67 | C00027 | https://www.genome.jp/entry/C00027 | Hydrogen peroxide | <0.001 | 0.001 | 2.075 | UP |
| 68 | C00460 | https://www.genome.jp/entry/C00460 | Deoxyuridine triphosphate | <0.001 | <0.001 | 1.917 | UP |
| 69 | C05379 | https://www.genome.jp/entry/C05379 | Oxalosuccinic acid | 0.001 | 0.003 | 1.978 | UP |
| 70 | C04409 | https://www.genome.jp/entry/C04409 | 2-Amino-3-carboxymuconic acid semialdehyde | 0.004 | 0.010 | 2.168 | UP |
| 71 | C00506 | https://www.genome.jp/entry/C00506 | Cysteic acid | 0.003 | 0.008 | 2.102 | UP |
| 72 | C05403 | https://www.genome.jp/entry/C05403 | 3'-Ketolactose | 0.001 | 0.003 | 2.258 | UP |
| 73 | C00322 | https://www.genome.jp/entry/C00322 | Oxoadipic acid | 0.002 | 0.006 | 1.927 | UP |
| 74 | C05335 | https://www.genome.jp/entry/C05335 | Selenomethionine | 0.001 | 0.003 | 3.084 | UP |
| 75 | C01345 | https://www.genome.jp/entry/C01345 | dITP | 0.004 | 0.012 | 2.419 | UP |
| 76 | C14872 | https://www.genome.jp/entry/C14872 | Thiodiacetic acid | <0.001 | 0.002 | 2.173 | UP |
| 77 | C00155 | https://www.genome.jp/entry/C00155 | L-Homocysteine | 0.02 | 0.042 | 1.651 | UP |
| 78 | C03415 | https://www.genome.jp/entry/C03415 | N2-Succinyl-L-ornithine | 0.021 | 0.043 | 1.721 | UP |
| 79 | C00603 | https://www.genome.jp/entry/C00603 | (S)-Ureidoglycolic acid | 0.017 | 0.037 | 1.655 | UP |
| 80 | C00387 | https://www.genome.jp/entry/C00387 | Guanosine | 0.038 | 0.069 | 1.648 | UP |
| 81 | C14854 | https://www.genome.jp/entry/C14854 | 9-Hydroxybenzo[a]pyrene-4,5-oxide | 0.042 | 0.075 | 1.662 | UP |
| 82 | C05841 | https://www.genome.jp/entry/C05841 | Nicotinate D-ribonucleoside | <0.001 | 0.002 | 1.931 | UP |
| 83 | C00053 | https://www.genome.jp/entry/C00053 | Phosphoadenosine phosphosulfate | 0.041 | 0.073 | 1.794 | UP |
| 84 | C14875 | https://www.genome.jp/entry/C14875 | S-(2-Hydroxyethyl)glutathione | 0.022 | 0.045 | 2.015 | UP |
| 85 | C03410 | https://www.genome.jp/entry/C03410 | N-Glycolylneuraminic acid | 0.014 | 0.030 | 1.56 | UP |
| 86 | C02220 | https://www.genome.jp/entry/C02220 | 2-Aminomuconic acid | 0.025 | 0.049 | 1.671 | UP |

| | | | | | | | |
|----|--------|---|--------------------------------|-------|-------|-------|----|
| 87 | C11132 | https://www.genome.jp/entry/C11132 | 2-Methoxyestrone 3-glucuronide | 0.039 | 0.071 | 1.356 | UP |
| 88 | C00169 | https://www.genome.jp/entry/C00169 | Carbamoyl phosphate | 0.006 | 0.016 | 1.135 | UP |
| 89 | C02470 | https://www.genome.jp/entry/C02470 | Xanthurenic acid | 0.026 | 0.051 | 1.588 | UP |
| 90 | C06429 | https://www.genome.jp/entry/C06429 | Docosahexaenoic acid | 0.021 | 0.042 | 4.787 | UP |
| 91 | C01044 | https://www.genome.jp/entry/C01044 | N-Formyl-L-aspartate | 0.039 | 0.070 | 1.853 | UP |
| 92 | C01417 | https://www.genome.jp/entry/C01417 | Cyanate | 0.008 | 0.020 | 1.193 | UP |

Table S2. VIP scores of metabolites.

| No | KEGG ID | Name | VIP score |
|----|---------|---|-----------|
| 1 | C09640 | (-)-Salsoline | 1.439 |
| 2 | C16613 | 6-Thiourate | 1.427 |
| 3 | C01211 | Procollagen 5-hydroxy-L-lysine | 1.419 |
| 4 | C00120 | Biotin | 1.415 |
| 5 | C03087 | 5-Acetamidovalerate | 1.395 |
| 6 | C01449 | Queuine | 1.392 |
| 7 | C05933 | N(omega)-Hydroxyarginine | 1.323 |
| 8 | C05401 | Galactosylglycerol | 1.311 |
| 9 | C00670 | Glycerophosphocholine | 1.298 |
| 10 | C01595 | Linoleic acid | 1.298 |
| 11 | C00957 | 3-Mercaptopyruvic acid | 1.295 |
| 12 | C02218 | 2-Aminoacrylic acid | 1.286 |
| 13 | C02576 | Perillyl aldehyde | 1.283 |
| 14 | C08012 | Levomethadyl Acetate | 1.274 |
| 15 | C00093 | Glycerol 3-phosphate | 1.250 |
| 16 | C00664 | 5-Formiminotetrahydrofolic acid | 1.249 |
| 17 | C05823 | 3-Mercaptolactic acid | 1.245 |
| 18 | C04441 | 2-(3-Carboxy-3-aminopropyl)-L-histidine | 1.245 |
| 19 | C00086 | Urea | 1.236 |
| 20 | C00390 | QH2 | 1.230 |
| 21 | C00850 | Aryl sulfate; Phenol sulfate | 1.219 |
| 22 | C03033 | 3-Methoxy-4-hydroxyphenylglycol glucuronide | 1.214 |
| 23 | C01031 | S-Formylglutathione | 1.212 |
| 24 | C03406 | Argininosuccinic acid | 1.207 |
| 25 | C06423 | Caprylic acid | 1.195 |
| 26 | C02325 | Sinapyl alcohol | 1.189 |
| 27 | C01152 | 1-Methylhistidine | 1.158 |
| 28 | C07535 | Benzo[a]pyrene | 1.147 |
| 29 | C16014 | cis-stilbene oxide | 1.140 |
| 30 | C05504 | Estriol-16-Glucuronide | 1.135 |
| 31 | C00037 | Glycine | 1.126 |
| 32 | C00245 | Taurine | 1.113 |
| 33 | C00864 | Pantothenic acid | 1.097 |
| 34 | C05552 | Biocytin | 1.097 |
| 35 | C00353 | Geranylgeranyl-PP | 1.095 |
| 36 | C05839 | cis-beta-D-Glucosyl-2-hydroxycinnamate | 1.084 |
| 37 | C16015 | (+)-(1R,2R)-1,2-Diphenylethane-1,2-diol | 1.070 |
| 38 | C05985 | 2-Propyn-1-al | 1.063 |
| 39 | C05588 | Metanephrine | 1.046 |
| 40 | C14852 | Benzo[a]pyrene-7,8-diol | 1.042 |
| 41 | C02727 | N6-Acetyl-L-lysine | 1.041 |
| 42 | C00409 | Methanethiol | 1.021 |
| 43 | C03492 | D-4'-Phosphopantothenate | 1.011 |
| 44 | C06755 | Chloroacetic acid | 0.990 |
| 45 | C00988 | Phosphoglycolic acid | 0.980 |

| | | | |
|----|--------|--|-------|
| 46 | C16632 | alpha-Fluoro-beta-alanine | 0.966 |
| 47 | C03078 | 4-Guanidinobutanamide | 0.959 |
| 48 | C01119 | Oxidized dithiothreitol | 0.958 |
| 49 | C00327 | Citrulline | 0.955 |
| 50 | C03413 | N1,N12-Diacetylspermine | 0.949 |
| 51 | C00058 | Formic acid | 0.948 |
| 52 | C02373 | 3a,7b,12a-Trihydroxy-5a-Cholanoic acid | 0.927 |
| 53 | C03340 | L-2,3-Dihydrodipicolinate | 0.920 |
| 54 | C08261 | Azelaic acid | 0.906 |
| 55 | C00440 | 5-Methyltetrahydrofolic acid | 0.886 |
| 56 | C16662 | L-alpha-Acetyl-N,N-dinormethadol | 0.873 |
| 57 | C04352 | 4'-Phosphopantothenoylcysteine | 0.862 |
| 58 | C06350 | Tetrahydropapaveroline; (R,S)-Norlaudanoline; Norlaudanoline | 0.855 |
| 59 | C00621 | Dolichyl diphosphate | 0.853 |
| 60 | C15650 | 5-(Methylthio)-2,3-dioxopentyl phosphate | 0.852 |
| 61 | C03356 | 3-Phospho-D-erythronate | 0.847 |
| 62 | C00073 | L-Methionine | 0.817 |
| 63 | C01620 | Threonic acid | 0.816 |
| 64 | C02637 | 3-Dehydroshikimate | 0.812 |
| 65 | C06206 | Benzoyl phosphate | 0.797 |
| 66 | C14873 | Thiodiacetic acid sulfoxide | 0.781 |
| 67 | C00027 | Hydrogen peroxide | 0.764 |
| 68 | C00460 | Deoxyuridine triphosphate | 0.747 |
| 69 | C05379 | Oxalosuccinic acid | 0.738 |
| 70 | C04409 | 2-Amino-3-carboxymuconic acid semialdehyde | 0.733 |
| 71 | C00506 | Cysteic acid | 0.720 |
| 72 | C05403 | 3'-Ketolactose | 0.716 |
| 73 | C00322 | Oxoadipic acid | 0.660 |
| 74 | C05335 | Selenomethionine | 0.645 |
| 75 | C01345 | dITP | 0.640 |
| 76 | C14872 | Thiodiacetic acid | 0.636 |
| 77 | C00155 | L-Homocysteine | 0.615 |
| 78 | C03415 | N2-Succinyl-L-ornithine | 0.613 |
| 79 | C00603 | (S)-Ureidoglycolic acid | 0.602 |
| 80 | C00387 | Guanosine | 0.578 |
| 81 | C14854 | 9-Hydroxybenzo[a]pyrene-4,5-oxide | 0.577 |
| 82 | C05841 | Nicotinate D-ribonucleoside | 0.575 |
| 83 | C00053 | Phosphoadenosine phosphosulfate | 0.574 |
| 84 | C14875 | S-(2-Hydroxyethyl)glutathione | 0.572 |
| 85 | C03410 | N-Glycolylneuraminic acid | 0.496 |
| 86 | C02220 | 2-Aminomuconic acid | 0.484 |
| 87 | C11132 | 2-Methoxyestrone 3-glucuronide | 0.470 |
| 88 | C00169 | Carbamoyl phosphate | 0.467 |
| 89 | C02470 | Xanthurenic acid | 0.465 |
| 90 | C06429 | Docosahexaenoic acid | 0.382 |
| 91 | C01044 | N-Formyl-L-aspartate | 0.377 |
| 92 | C01417 | Cyanate | 0.335 |

Pathway enrichment analysis was also conducted on CPDB since this software simultaneously considers several databases in addition to KEGG. The results of enrichment analysis for Metaboanalyst and CPDB are shown in Tables S3 and S4.

Table S3. Results of pathway enrichment analysis conducted on MetaboAnalyst based on KEGG database.

| Pathway | Total | Hits | p-value |
|---|--------------|-------------|----------------|
| Biotin metabolism | 10 | 2 | 0.012 |
| Cysteine and methionine metabolism | 33 | 3 | 0.019 |
| Arginine biosynthesis | 14 | 2 | 0.024 |
| Pantothenate and CoA biosynthesis | 20 | 2 | 0.046 |
| Linoleic acid metabolism | 5 | 1 | 0.085 |
| Glycerophospholipid metabolism | 36 | 2 | 0.130 |
| Taurine and hypotaurine metabolism | 8 | 1 | 0.132 |
| Sulfur metabolism | 8 | 1 | 0.132 |
| One carbon pool by folate | 9 | 1 | 0.148 |
| Primary bile acid biosynthesis | 46 | 2 | 0.192 |
| Glycerolipid metabolism | 16 | 1 | 0.248 |
| Ubiquinone and other terpenoid-quinone biosynthesis | 18 | 1 | 0.274 |
| Terpenoid backbone biosynthesis | 18 | 1 | 0.274 |
| Ether lipid metabolism | 20 | 1 | 0.300 |
| Metabolism of xenobiotics by cytochrome P450 | 68 | 2 | 0.337 |
| Galactose metabolism | 27 | 1 | 0.382 |
| Alanine, aspartate and glutamate metabolism | 28 | 1 | 0.393 |
| Glutathione metabolism | 28 | 1 | 0.393 |
| Lipoic acid metabolism | 28 | 1 | 0.393 |
| Lysine degradation | 30 | 1 | 0.415 |
| Glyoxylate and dicarboxylate metabolism | 31 | 1 | 0.425 |
| Porphyrin metabolism | 31 | 1 | 0.425 |
| Glycine, serine and threonine metabolism | 33 | 1 | 0.446 |
| Arginine and proline metabolism | 36 | 1 | 0.475 |
| Biosynthesis of unsaturated fatty acids | 36 | 1 | 0.475 |
| Drug metabolism - other enzymes | 39 | 1 | 0.503 |
| Fatty acid biosynthesis | 47 | 1 | 0.570 |
| Drug metabolism - cytochrome P450 | 55 | 1 | 0.629 |
| Purine metabolism | 70 | 1 | 0.719 |
| Steroid hormone biosynthesis | 87 | 1 | 0.795 |

Table S4. Results of pathway enrichment analysis conducted on CPDB based on multiple databases.

| Pathway | Total | Hits | p-value | Database |
|---|-------|------|---------|--------------|
| Methionine and cysteine metabolism | 80 | 5 | 0.001 | EHMN |
| Amino acid conjugation | 6 | 2 | 0.001 | Wikipathways |
| Lysine degradation - Homo sapiens (human) | 50 | 4 | 0.001 | KEGG |
| Hyperornithinemia with gyrate atrophy (HOGA) | 52 | 4 | 0.001 | SMPDB |
| Creatine deficiency, guanidinoacetate methyltransferase deficiency | 52 | 4 | 0.001 | SMPDB |
| L-arginine:glycine amidinotransferase deficiency | 52 | 4 | 0.001 | SMPDB |
| Hyperornithinemia-hyperammonemia-homocitrullinuria [HHH-syndrome] | 52 | 4 | 0.001 | SMPDB |
| Guanidinoacetate Methyltransferase Deficiency (GAMT Deficiency) | 52 | 4 | 0.001 | SMPDB |
| Prolinemia Type II | 52 | 4 | 0.001 | SMPDB |
| Prolidase Deficiency (PD) | 52 | 4 | 0.001 | SMPDB |
| Arginine and Proline Metabolism | 52 | 4 | 0.001 | SMPDB |
| Hyperprolinemia Type I | 52 | 4 | 0.001 | SMPDB |
| Hyperprolinemia Type II | 52 | 4 | 0.001 | SMPDB |
| Ornithine Aminotransferase Deficiency (OAT Deficiency) | 52 | 4 | 0.001 | SMPDB |
| Arginine: Glycine Amidinotransferase Deficiency (AGAT Deficiency) | 52 | 4 | 0.001 | SMPDB |
| Metabolism of vitamins and cofactors | 188 | 6 | 0.001 | Reactome |
| Metabolism of water-soluble vitamins and cofactors | 125 | 5 | 0.001 | Reactome |
| Biotin Metabolism | 7 | 2 | 0.002 | SMPDB |
| Multiple carboxylase deficiency, neonatal or early onset form | 7 | 2 | 0.002 | SMPDB |
| Biotinidase Deficiency | 7 | 2 | 0.002 | SMPDB |
| Biotin metabolism - Homo sapiens (human) | 28 | 3 | 0.002 | KEGG |
| SLC-mediated transmembrane transport | 164 | 6 | 0.002 | Reactome |
| Hydrolysis of LPC | 9 | 2 | 0.002 | Reactome |
| Glycerophospholipid catabolism | 11 | 2 | 0.002 | Reactome |
| Cysteine and methionine metabolism - Homo sapiens (human) | 63 | 4 | 0.002 | KEGG |
| Biotin transport and metabolism | 9 | 2 | 0.003 | Reactome |
| Arginine Proline metabolism | 68 | 4 | 0.003 | INOH |
| Degradation of cysteine and homocysteine | 40 | 3 | 0.003 | Reactome |
| Choline metabolism in cancer - Homo sapiens (human) | 11 | 2 | 0.004 | KEGG |
| Vitamin H (biotin) metabolism | 11 | 2 | 0.004 | EHMN |
| Metabolism of amino acids and derivatives | 286 | 7 | 0.004 | Reactome |
| Vitamin digestion and absorption - Homo sapiens (human) | 39 | 3 | 0.004 | KEGG |
| Biochemical Pathways Part I | 469 | 10 | 0.005 | Wikipathways |
| Coenzyme A biosynthesis | 13 | 2 | 0.005 | Reactome |
| coenzyme A biosynthesis | 13 | 2 | 0.005 | HumanCyc |
| glutathione-mediated detoxification | 14 | 2 | 0.006 | HumanCyc |
| ABC transporters - Homo sapiens (human) | 138 | 5 | 0.006 | KEGG |
| Transport of small molecules | 219 | 6 | 0.006 | Reactome |
| Methionine Cysteine metabolism | 45 | 3 | 0.007 | INOH |
| Glycerophospholipid metabolism | 95 | 4 | 0.009 | EHMN |
| Pyruvate Carboxylase Deficiency | 17 | 2 | 0.009 | SMPDB |
| Primary Hyperoxaluria Type I | 17 | 2 | 0.009 | SMPDB |
| Lactic Acidemia | 17 | 2 | 0.009 | SMPDB |
| Alanine Metabolism | 17 | 2 | 0.009 | SMPDB |
| urea cycle | 17 | 2 | 0.009 | HumanCyc |
| Vitamin B5 (pantothenate) metabolism | 17 | 2 | 0.009 | Reactome |
| Metabolism | 1411 | 15 | 0.010 | Reactome |
| Sulfur amino acid metabolism | 67 | 3 | 0.011 | Reactome |
| Fatty Acid Biosynthesis | 33 | 2 | 0.012 | SMPDB |
| Methionine metabolism leading to sulfur amino acids and related disorders | 21 | 2 | 0.012 | Wikipathways |
| Amino Acid metabolism | 108 | 4 | 0.013 | Wikipathways |
| Recycling of bile acids and salts | 20 | 2 | 0.013 | Reactome |
| Pantothenate and CoA Biosynthesis | 21 | 2 | 0.014 | SMPDB |
| Vitamin B5 - CoA biosynthesis from pantothenate | 21 | 2 | 0.014 | EHMN |

| | | | | |
|---|-----|---|-------|--------------|
| Arginine biosynthesis - Homo sapiens (human) | 23 | 2 | 0.017 | KEGG |
| Urea cycle | 23 | 2 | 0.017 | Reactome |
| Transport of vitamins, nucleosides, and related molecules | 63 | 3 | 0.017 | Reactome |
| Disorders of Folate Metabolism and Transport | 26 | 2 | 0.020 | Wikipathways |
| PI Metabolism | 29 | 2 | 0.020 | Reactome |
| Glycine Serine metabolism | 68 | 3 | 0.021 | INOH |
| Beta-mercaptolactate-cysteine disulfiduria | 26 | 2 | 0.021 | SMPDB |
| Cysteine Metabolism | 26 | 2 | 0.021 | SMPDB |
| Cystinosis, ocular nonnephropathic | 26 | 2 | 0.021 | SMPDB |
| Urea cycle and metabolism of arginine, proline, glutamate, aspartate and asparagine | 125 | 4 | 0.022 | EHMN |
| Argininemia | 27 | 2 | 0.023 | SMPDB |
| Citrullinemia Type I | 27 | 2 | 0.023 | SMPDB |
| Carbamoyl Phosphate Synthetase Deficiency | 27 | 2 | 0.023 | SMPDB |
| Argininosuccinic Aciduria | 27 | 2 | 0.023 | SMPDB |
| Urea Cycle | 27 | 2 | 0.023 | SMPDB |
| Ornithine Transcarbamylase Deficiency (OTC Deficiency) | 27 | 2 | 0.023 | SMPDB |
| Transport of bile salts and organic acids, metal ions and amine compounds | 79 | 3 | 0.023 | Reactome |
| Na ⁺ /Cl ⁻ dependent neurotransmitter transporters | 32 | 2 | 0.024 | Reactome |
| Glutathione conjugation | 31 | 2 | 0.024 | Reactome |
| Amino acid transport across the plasma membrane | 32 | 2 | 0.026 | Reactome |
| Ammonia Recycling | 29 | 2 | 0.026 | SMPDB |
| Pantothenate and CoA biosynthesis - Homo sapiens (human) | 30 | 2 | 0.028 | KEGG |
| Trans-sulfuration and one-carbon metabolism | 33 | 2 | 0.029 | Wikipathways |
| Urea cycle and metabolism of amino groups | 32 | 2 | 0.029 | Wikipathways |
| Pyruvate dehydrogenase deficiency (E3) | 33 | 2 | 0.031 | SMPDB |
| Pyruvate dehydrogenase deficiency (E2) | 33 | 2 | 0.031 | SMPDB |
| 2-ketoglutarate dehydrogenase complex deficiency | 33 | 2 | 0.031 | SMPDB |
| Mitochondrial complex II deficiency | 33 | 2 | 0.031 | SMPDB |
| Fumarase deficiency | 33 | 2 | 0.031 | SMPDB |
| Congenital lactic acidosis | 33 | 2 | 0.031 | SMPDB |
| Citric Acid Cycle | 33 | 2 | 0.031 | SMPDB |
| beta-Alanine metabolism - Homo sapiens (human) | 32 | 2 | 0.031 | KEGG |
| triacylglycerol degradation | 54 | 2 | 0.031 | HumanCyc |
| Sulfur metabolism - Homo sapiens (human) | 33 | 2 | 0.033 | KEGG |
| Carnosinuria, carnosinemia | 34 | 2 | 0.033 | SMPDB |
| Ureidopropionase deficiency | 34 | 2 | 0.033 | SMPDB |
| GABA-Transaminase Deficiency | 34 | 2 | 0.033 | SMPDB |
| Beta-Alanine Metabolism | 34 | 2 | 0.033 | SMPDB |
| phospholipases | 55 | 2 | 0.035 | HumanCyc |
| sphingomyelin metabolism/ceramide salvage | 55 | 2 | 0.035 | HumanCyc |
| Vitamin B9 (folate) metabolism | 35 | 2 | 0.037 | EHMN |
| Citrate cycle | 35 | 2 | 0.037 | INOH |
| Lysine degradation | 36 | 2 | 0.039 | INOH |
| Glycerolipid metabolism - Homo sapiens (human) | 38 | 2 | 0.043 | KEGG |
| The oncogenic action of 2-hydroxyglutarate | 40 | 2 | 0.045 | SMPDB |
| Histidine Metabolism | 40 | 2 | 0.045 | SMPDB |
| Histidinemia | 40 | 2 | 0.045 | SMPDB |
| the visual cycle I (vertebrates) | 58 | 2 | 0.045 | HumanCyc |
| The oncogenic action of Succinate | 41 | 2 | 0.047 | SMPDB |
| The oncogenic action of L-2-hydroxyglutarate in Hydroxyglutaricaciduria | 41 | 2 | 0.047 | SMPDB |
| The oncogenic action of D-2-hydroxyglutarate in Hydroxyglutaricaciduria | 41 | 2 | 0.047 | SMPDB |
| sphingosine and sphingosine-1-phosphate metabolism | 59 | 2 | 0.047 | HumanCyc |
| The oncogenic action of Fumarate | 42 | 2 | 0.049 | SMPDB |