**LC-MS Metabolomics Methods**

Sectioned and weighed frozen liver tissue samples (n=175, 60-450 mg) were homogenized with cold methanol (10 µl for every mg of tissue) in a Bead Ruptor Elite Bead Mill Homogenizer (OMNI International) at 5.0 m/s for 30 s in two cycles. The supernatants were collected after centrifugation at 16,000 rcf for 20 min at 4 °C. A quality control pool (QC pool) sample was prepared by pooling 30 µL supernatant aliquots from selected individual samples (n=78), with a total pre-processing weight ≥ 60 mg. The supernatants (200 µL) of each study sample and QC pools were transferred to new tubes and dried under Speed-vac. Each dried sample was reconstituted in a 200 µL water-methanol (95:5) solution containing 500 ng/ml L-tryphotophan-d5. The samples were thoroughly mixed on multiple tube vortexer for 10 mins at 5000 rpm. Samples were centrifuged at room temperature and at 16,000 rcffor 4 min. The supernatant was transferred to pre-labeled auto-sampler vials for data acquisition.

Untargeted metabolomics was conducted using a Thermo Scientific™ Vanquish™ UPHPLC - Q Exactive™ HF-X Orbitrap System. Metabolites were separated on an Acquity UPLC HSS T3 C18 (2.1 X 100 mm, 1.8 µm) operating at 50 °C using a reversed phase gradient separation with Water with 0.1% Formic Acid (v/v) as mobile phase A and Methanol with 0.1% Formic Acid (v/v) as mobile phase B. A 5 µL amount was injected into the instrument, and MS data was collected between 50-750 m/z in the positive mode with the MS/MS data triggered by the Data-Dependent Acquisition.

**Table 1.** Sample Acquisition Information

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Prep Order** | **DRCC ID** | **Liver Lobe** | **Diet** | **Tissue Weight (g)** |
| 1 | L\_59 | Left | HP | 0.0619 |
| 2 | L\_87 | Median | HCHF | 0.0767 |
| 3 | L\_85 | Right | HCHF | 0.0786 |
| 4 | L\_36 | Median | HCHF | 0.1082 |
| 5 | L\_156 | Median | HCHF | 0.0415 |
| 6 | L\_177 | Median | HP | 0.0585 |
| 7 | L\_67 | Right | HP | 0.0656 |
| 8 | L\_93 | Median | HCHF | 0.0210 |
| 9 | L\_11 | Left | HP | 0.0404 |
| 10 | L\_72 | Median | HP | 0.0328 |
| 11 | L\_134 | Left | HP | 0.0681 |
| 13 | L\_164 | Left | HP | 0.0465 |
| 14 | L\_120 | Median | HP | 0.0269 |
| 15 | L\_96 | Median | HCHF | 0.1322 |
| 16 | L\_139 | Right | HP | 0.0741 |
| 17 | L\_54 | Median | HP | 0.0458 |
| 18 | L\_7 | Right | HP | 0.0481 |
| 19 | L\_56 | Left | HP | 0.0445 |
| 20 | L\_16 | Right | HP | 0.0531 |
| 21 | L\_163 | Right | HP | 0.0351 |
| 22 | L\_98 | Left | HCHF | 0.0448 |
| 24 | L\_77 | Left | HCHF | 0.0778 |
| 25 | L\_27 | Median | HCHF | 0.2022 |
| 26 | L\_166 | Right | HP | 0.0745 |
| 27 | L\_28 | Right | HCHF | 0.3301 |
| 28 | L\_57 | Median | HP | 0.0434 |
| 29 | L\_95 | Left | HCHF | 0.0256 |
| 30 | L\_55 | Right | HP | 0.0645 |
| 31 | L\_86 | Left | HCHF | 0.0816 |
| 32 | L\_115 | Right | HP | 0.0525 |
| 33 | L\_82 | Right | HP | 0.0753 |
| 34 | L\_104 | Left | HCHF | 0.0365 |
| 35 | L\_83 | Left | HP | 0.0447 |
| 36 | L\_138 | Median | HP | 0.0190 |
| 37 | L\_167 | Left | HP | 0.0333 |
| 39 | L\_100 | Right | HCHF | 0.0618 |
| 40 | L\_140 | Left | HP | 0.0422 |
| 41 | L\_105 | Median | HCHF | 0.1330 |
| 42 | L\_61 | Right | HP | 0.0789 |
| 43 | L\_39 | Median | HCHF | 0.2002 |
| 44 | L\_43 | Right | HCHF | 0.1593 |
| 45 | L\_31 | Right | HCHF | 0.2365 |
| 46 | L\_110 | Left | HCHF | 0.0684 |
| 47 | L\_15 | Median | HP | 0.0068 |
| 48 | L\_107 | Left | HCHF | 0.0343 |
| 49 | L\_109 | Right | HCHF | 0.0637 |
| 50 | L\_12 | Median | HP | 0.0032 |
| 51 | L\_127 | Right | HP | 0.0659 |
| 52 | L\_8 | Left | HP | 0.0443 |
| 53 | L\_111 | Median | HCHF | 0.1385 |
| 54 | L\_26 | Left | HCHF | 0.1162 |
| 55 | L\_170 | Left | HP | 0.0619 |
| 56 | L\_145 | Right | HCHF | 0.0855 |
| 57 | L\_119 | Left | HP | 0.0147 |
| 58 | L\_92 | Left | HCHF | 0.0258 |
| 59 | L\_5 | Left | HP | 0.0613 |
| 60 | L\_144 | Median | HP | 0.0465 |
| 61 | L\_90 | Median | HCHF | 0.1930 |
| 62 | L\_73 | Right | HCHF | 0.0767 |
| 63 | L\_178 | Right | HP | 0.0745 |
| 64 | L\_142 | Right | HP | 0.0508 |
| 65 | L\_6 | Median | HP | 0.0397 |
| 66 | L\_94 | Right | HCHF | 0.0680 |
| 67 | L\_112 | Right | HCHF | 0.0724 |
| 68 | L\_22 | Right | HP | 0.0521 |
| 69 | L\_158 | Left | HCHF | 0.0764 |
| 70 | L\_165 | Median | HP | 0.0319 |
| 71 | L\_159 | Median | HCHF | 0.0845 |
| 72 | L\_154 | Right | HCHF | 0.1238 |
| 73 | L\_19 | Right | HP | 0.0500 |
| 74 | L\_132 | Median | HP | 0.0697 |
| 75 | L\_81 | Median | HP | 0.0415 |
| 76 | L\_131 | Left | HP | 0.0207 |
| 77 | L\_41 | Left | HCHF | 0.1336 |
| 78 | L\_38 | Left | HCHF | 0.0456 |
| 80 | L\_76 | Right | HCHF | 0.0650 |
| 81 | L\_17 | Left | HP | 0.0470 |
| 82 | L\_47 | Left | HCHF | 0.0854 |
| 83 | L\_174 | Median | HP | 0.0277 |
| 84 | L\_25 | Right | HCHF | 0.3393 |
| 85 | L\_49 | Right | HP | 0.0677 |
| 86 | L\_62 | Left | HP | 0.0885 |
| 87 | L\_162 | Median | HCHF | 0.0342 |
| 88 | L\_116 | Left | HP | 0.0112 |
| 89 | L\_172 | Right | HP | 0.0818 |
| 90 | L\_24 | Median | HP | 0.0106 |
| 91 | L\_176 | Left | HP | 0.0530 |
| 92 | L\_23 | Left | HP | 0.0152 |
| 93 | L\_147 | Median | HCHF | 0.0508 |
| 94 | L\_68 | Left | HP | 0.0394 |
| 95 | L\_65 | Left | HP | 0.0318 |
| 96 | L\_40 | Right | HCHF | 0.1442 |
| 97 | L\_169 | Right | HP | 0.0695 |
| 98 | L\_155 | Left | HCHF | 0.0350 |
| 99 | L\_88 | Right | HCHF | 0.0681 |
| 100 | L\_75 | Median | HCHF | 0.0297 |
| 101 | L\_3 | Median | HP | 0.0094 |
| 102 | L\_2 | Left | HP | 0.0528 |
| 103 | L\_21 | Median | HP | 0.0138 |
| 104 | L\_175 | Right | HP | 0.0644 |
| 105 | L\_137 | Left | HP | 0.0262 |
| 106 | L\_60 | Median | HP | 0.0380 |
| 107 | L\_10 | Right | HP | 0.0650 |
| 108 | L\_63 | Median | HP | 0.0488 |
| 109 | L\_9 | Median | HP | 0.0189 |
| 110 | L\_4 | Right | HP | 0.0449 |
| 111 | L\_179 | Left | HP | 0.0530 |
| 112 | L\_74 | Left | HCHF | 0.0466 |
| 113 | L\_64 | Right | HP | 0.0573 |
| 114 | L\_33 | Median | HCHF | 0.1212 |
| 115 | L\_101 | Left | HCHF | 0.0329 |
| 116 | L\_35 | Left | HCHF | 0.0896 |
| 117 | L\_123 | Median | HP | 0.0143 |
| 118 | L\_124 | Right | HP | 0.0895 |
| 119 | L\_34 | Right | HCHF | 0.2467 |
| 120 | L\_14 | Left | HP | 0.0146 |
| 121 | L\_135 | Median | HP | 0.0247 |
| 122 | L\_58 | Right | HP | 0.0545 |
| 123 | L\_69 | Median | HP | 0.0383 |
| 124 | L\_66 | Median | HP | 0.0475 |
| 125 | L\_133 | Right | HP | 0.0712 |
| 126 | L\_91 | Right | HCHF | 0.2016 |
| 127 | L\_13 | Right | HP | 0.0459 |
| 128 | L\_70 | Right | HP | 0.0592 |
| 129 | L\_78 | Median | HCHF | 0.0769 |
| 130 | L\_118 | Right | HP | 0.0510 |
| 131 | L\_1 | Right | HP | 0.0480 |
| 132 | L\_122 | Left | HP | 0.0160 |
| 133 | L\_160 | Right | HCHF | 0.0929 |
| 134 | L\_121 | Right | HP | 0.0470 |
| 135 | L\_161 | Left | HCHF | 0.0500 |
| 136 | L\_103 | Right | HCHF | 0.0598 |
| 137 | L\_50 | Left | HP | 0.0361 |
| 138 | L\_143 | Left | HP | 0.0551 |
| 139 | L\_30 | Median | HCHF | 0.2022 |
| 140 | L\_37 | Right | HCHF | 0.0696 |
| 141 | L\_99 | Median | HCHF | 0.0266 |
| 142 | L\_44 | Left | HCHF | 0.1479 |
| 143 | L\_46 | Right | HCHF | 0.0982 |
| 144 | L\_29 | Left | HCHF | 0.1312 |
| 145 | L\_80 | Left | HP | 0.0417 |
| 146 | L\_168 | Median | HP | 0.0280 |
| 147 | L\_53 | Left | HP | 0.0474 |
| 148 | L\_42 | Median | HCHF | 0.4357 |
| 149 | L\_152 | Left | HCHF | 0.0670 |
| 150 | L\_79 | Right | HP | 0.0608 |
| 151 | L\_108 | Median | HCHF | 0.0558 |
| 152 | L\_153 | Median | HCHF | 0.0453 |
| 153 | L\_106 | Right | HCHF | 0.0966 |
| 154 | L\_20 | Left | HP | 0.0271 |
| 155 | L\_48 | Median | HCHF | 0.2765 |
| 156 | L\_32 | Left | HCHF | 0.0612 |
| 157 | L\_113 | Left | HCHF | 0.0659 |
| 158 | L\_150 | Median | HCHF | 0.0634 |
| 159 | L\_151 | Right | HCHF | 0.0986 |
| 160 | L\_51 | Median | HP | 0.0530 |
| 161 | L\_97 | Right | HCHF | 0.0477 |
| 162 | L\_180 | Median | HP | 0.0597 |
| 163 | L\_157 | Right | HCHF | 0.0820 |
| 164 | L\_146 | Left | HCHF | 0.0597 |
| 165 | L\_71 | Left | HP | 0.0420 |
| 166 | L\_171 | Median | HP | 0.0151 |
| 167 | L\_130 | Right | HP | 0.0547 |
| 168 | L\_114 | Median | HCHF | 0.0823 |
| 169 | L\_89 | Left | HCHF | 0.0371 |
| 170 | L\_45 | Median | HCHF | 0.3797 |
| 171 | L\_141 | Median | HP | 0.0252 |
| 172 | L\_84 | Median | HP | 0.0537 |
| 173 | L\_136 | Right | HP | 0.0244 |
| 174 | L\_149 | Left | HCHF | 0.0425 |
| 175 | L\_18 | Median | HP | 0.0207 |
| 176 | L\_52 | Right | HP | 0.0621 |
| 177 | L\_117 | Median | HP | 0.0983 |
| 178 | L\_148 | Right | HCHF | 0.1067 |
| 179 | L\_173 | Left | HP | 0.0402 |