# Supporting Information

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**Metabolic profiling of neocortical tissue discriminates Alzheimer's disease from mild cognitive impairment, high pathology controls, and normal controls**

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**Page S-14: Figure S8**. (A) Scores plot of PLS-DA model constructed using significant between-group metabolites (lauric acid, myristic acid, stearic acid, palmitic acid) in conjunction with highly correlated neuropathological characteristics (frontal plaque, total plaque, total tangle, and Braak score) ($R^2X$ = 0.710, $R^2Y$ = 0.748, $R^2Q$ = 0.722) and (B) Permutation testing with 100 iterations shows excellent model fit ($p$ < 0.01).

**Page S-15: Figure S9.** Network view of enzyme enrichment analysis conducted between case (MCI and AD) and control (NC and HPC). Enrichment ratios were significantly different for eleven enzymes between groups ($p$ < 0.05).

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**Table S1**. Matrix of correlation analysis between candidate markers and clinical characteristics showing *r* and (*p*).

| Clinical Characteristic | 272.2@20.932005 | 147.1@14.3080015 | 147.1@20.774895 | 73.1@27.868113 | Lauric acid | Myristic acid | Palmitoleic acid | Palmitic acid | Stearic acid |
|---|---|---|---|---|---|---|---|---|---|
| Age | -0.079 | 0.048 | -0.036 | -0.103 | -0.043 | 0.150 | 0.210 | 0.168 | 0.168 |
| | (0.598) | (0.748) | (0.810) | (0.490) | (0.775) | (0.313) | (0.157) | (0.259) | (0.259) |
| Sex | 0.116 | -0.246 | -0.012 | -0.100 | -0.071 | 0.104 | 0.234 | 0.181 | 0.136 |
| | (0.437) | (0.095) | (0.936) | (0.505) | (0.638) | (0.488) | (0.114) | (0.222) | (0.360) |
| PMI | 0.219 | 0.019 | 0.183 | -0.078 | -0.269 | -0.221 | -0.222 | -0.149 | -0.154 |
| | (0.139) | (0.897) | (0.217) | (0.604) | (0.067) | (0.135) | (0.134) | (0.318) | (0.302) |
| APOE alleles | -0.045 | 0.048 | -0.047 | -0.084 | 0.092 | 0.051 | 0.058 | 0.031 | 0.043 |
| | (0.762) | (0.751) | (0.755) | (0.574) | (0.538) | (0.733) | (0.699) | (0.839) | (0.777) |
| MMSE | -0.097 | 0.114 | -0.064 | 0.362 | 0.363 | 0.398 | 0.202 | 0.278 | 0.294 |
| | (0.515) | (0.445) | (0.669) | (0.012) | (0.012) | (0.006) | (0.172) | (0.059) | (0.045) |
| Frontal plaque | 0.198 | -0.036 | 0.130 | -0.160 | -0.598 | -0.085 | 0.118 | 0.003 | -0.004 |
| | (0.182) | (0.810) | (0.382) | (0.283) | (0.000) | (0.569) | (0.428) | (0.982) | (0.981) |
| Total Plaque | 0.296 | -0.092 | 0.157 | -0.153 | -0.579 | -0.100 | 0.108 | -0.001 | -0.002 |
| | (0.043) | (0.539) | (0.293) | (0.305) | (0.000) | (0.503) | (0.469) | (0.993) | (0.988) |
| Frontal Tangle | 0.203 | -0.129 | 0.070 | -0.141 | -0.410 | -0.399 | -0.109 | -0.289 | -0.276 |
| | (0.172) | (0.387) | (0.639) | (0.345) | (0.004) | (0.005) | (0.467) | (0.048) | (0.061) |
| Total Tangle | 0.111 | -0.200 | 0.148 | -0.246 | -0.507 | -0.350 | -0.011 | -0.219 | -0.229 |
| | (0.457) | (0.177) | (0.322) | (0.096) | (0.000) | (0.016) | (0.941) | (0.138) | (0.122) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Braak score | 0.063 | -0.157 | 0.198 | -0.252 | -0.539 | -0.353 | -0.046 | -0.234 | -0.250 |
| | (0.672) | (0.293) | (0.182) | (0.087) | (0.000) | (0.015) | (0.757) | (0.113) | (0.091) |
| Frontal CAA | 0.105 | 0.036 | 0.179 | -0.165 | -0.169 | 0.094 | 0.274 | 0.209 | 0.196 |
| | (0.481) | (0.811) | (0.228) | (0.267) | (0.257) | (0.529) | (0.063) | (0.159) | (0.187) |
| Total CAA | 0.100 | 0.005 | 0.083 | -0.164 | -0.211 | 0.091 | 0.295 | 0.219 | 0.194 |
| | (0.502) | (0.972) | (0.579) | (0.269) | (0.155) | (0.543) | (0.044) | (0.139) | (0.191) |

**Table S2.** Full list of significantly enriched enzymes in response to Alzheimer's progression. For analysis, subjects were dichotomously grouped as case (MCI and AD) and control (NC and HPC).

| Enzyme | *p* value |
|---|---|
| Mitochondrial 2-oxovalerate dehydrogenase | 0.025 |
| 3-amino-isobutyrate transport | 0.025 |
| Mitochondrial 3-amino-isobutyrate transport | 0.025 |
| 3-hydroxyacyl-CoA dehydratase | 0.025 |
| Mitochondrial 3-hydroxyisobutyrate dehydrogenase | 0.025 |
| Mitochondrial 3-hydroxyisobutyryl-CoA hydrolase | 0.025 |
| Mitochondrial acyl-CoA dehydrogenase | 0.025 |
| L-3-amino-isobutanoate exchange | 0.025 |
| Mitochondrial L-3-aminoisobutyrate transaminase | 0.025 |
| Mitochondrial malonate-semialdehyde dehydrogenase | 0.025 |
| Methylmalonate-semialdehyde dehydrogenase | 0.025 |

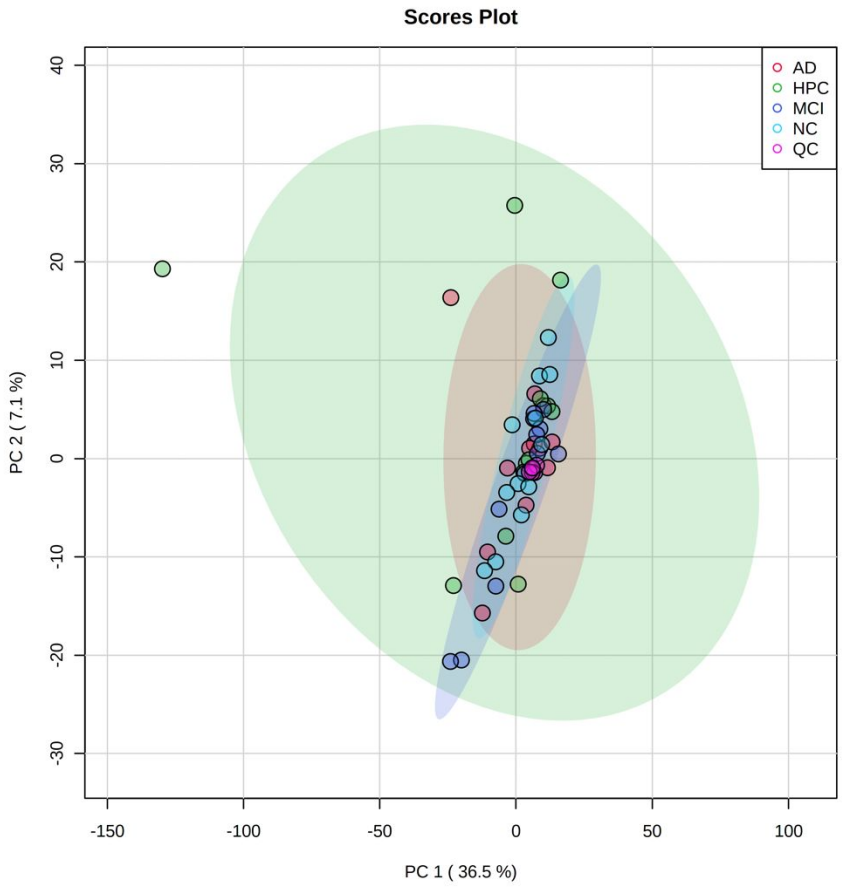
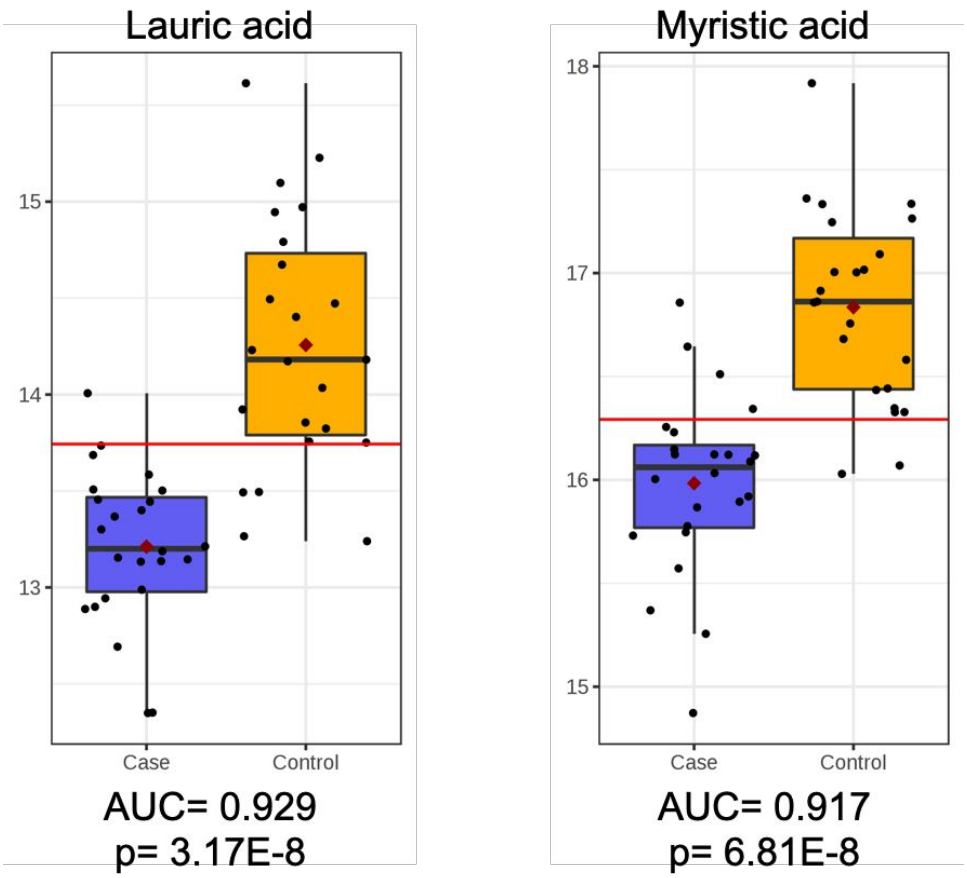



**Figure S1.** Scores plot of principal component analysis (PCA) conducted with all reliably detected metabolites between all groups, including quality control (QC) samples; 95% confidence intervals were evaluated for potential outliers. Data for sample 13 (HPC group) was reviewed and removed from further analysis.

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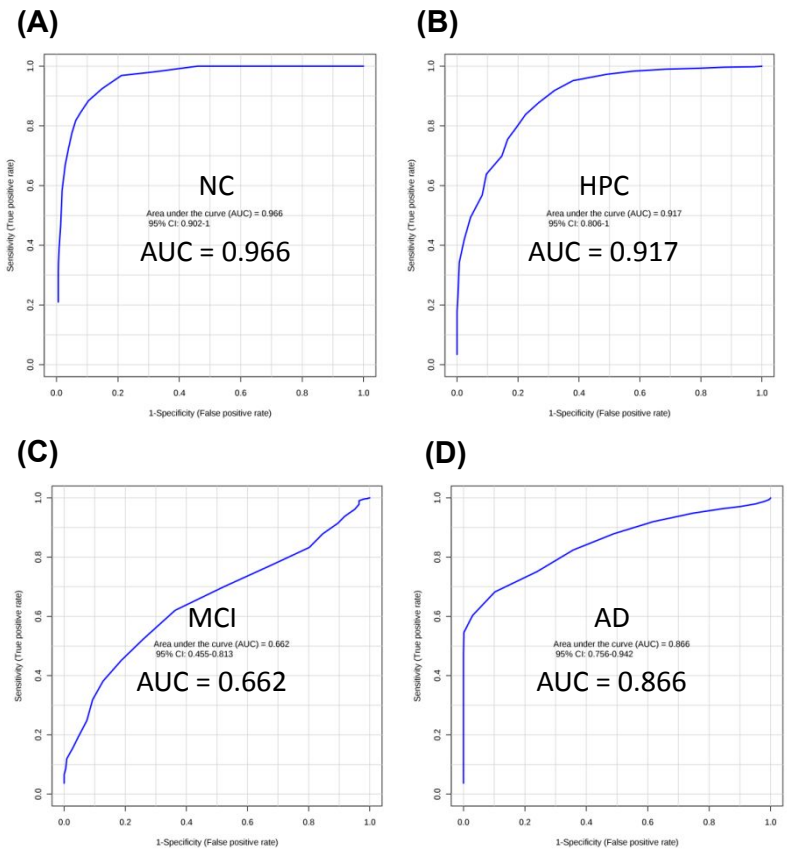


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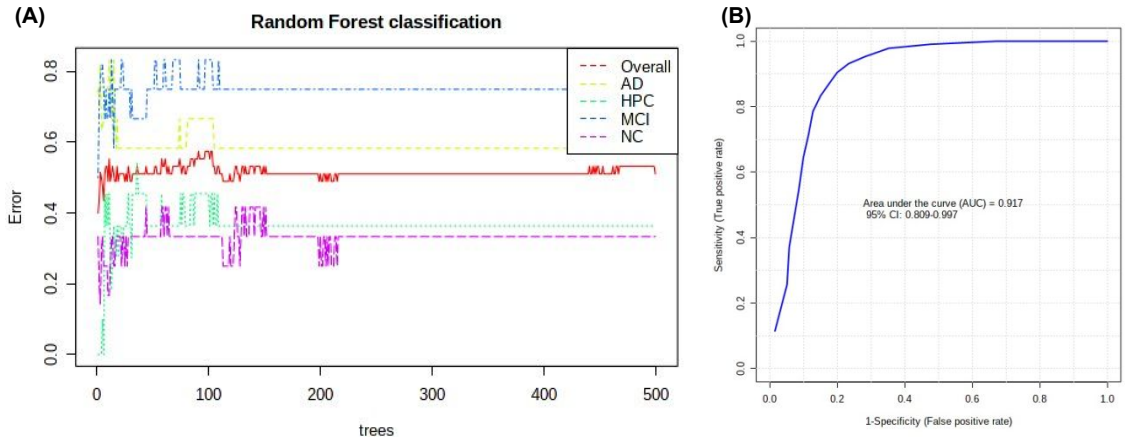



**Figure S4.** (A) RF analysis of study groups based on levels of lauric acid, myristic acid, stearic acid, palmitic acid (OOB error = 0.511), and (B) 100-fold LOOCV ROC analysis of case (MCI/AD) and control (NC/HPC) using RF classifier (AUC = 0.917).

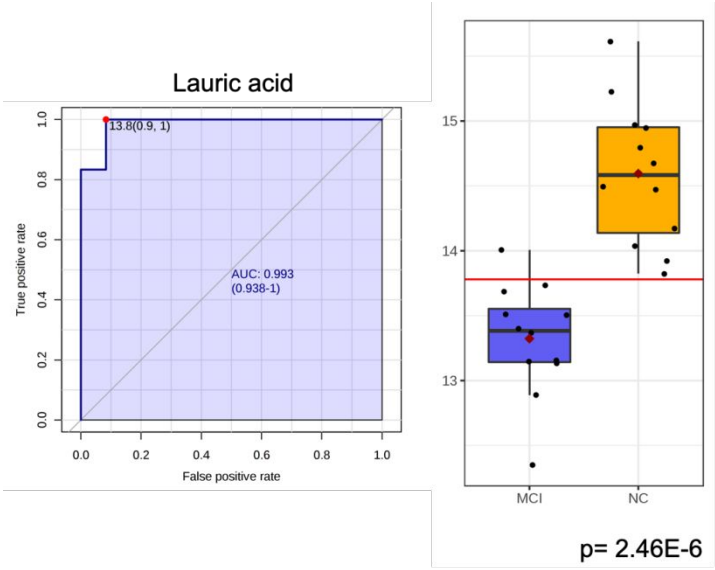



**Figure S5**. Univariate ROC analysis and t-testing between NC and MCI groups show lauric acid to be highly predictive (AUC = 0.993) and significant (FDR $q < 0.001$).

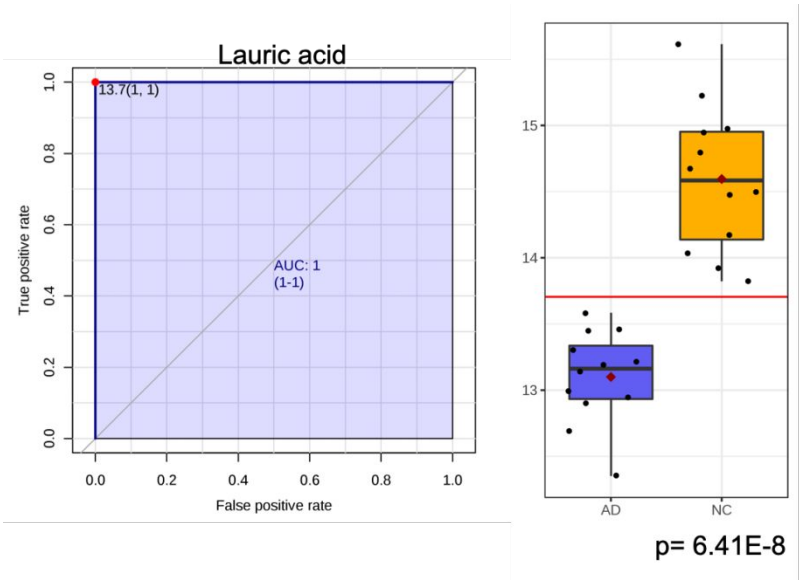
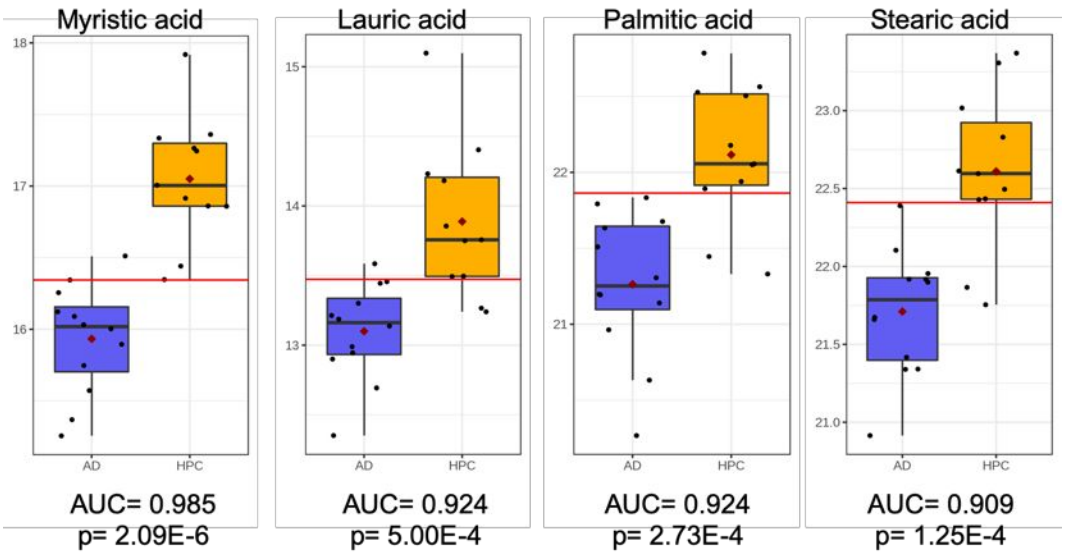



**Figure S6.** Univariate ROC analysis and t-testing between NC and AD groups show lauric acid to be highly predictive (AUC = 1.0) and significant (FDR $q < 0.001$).

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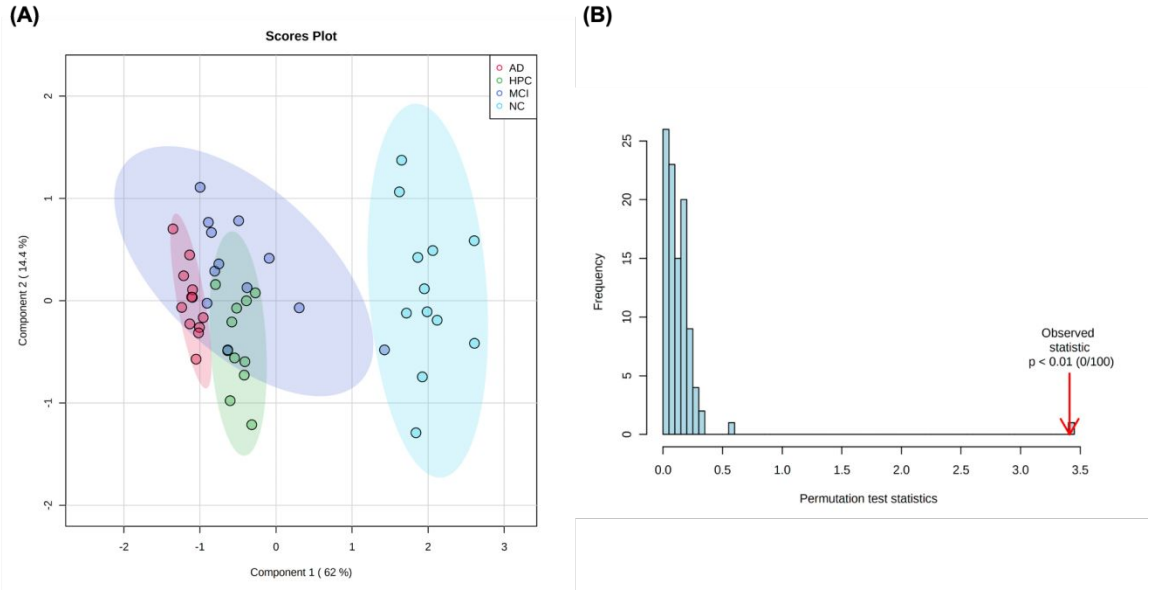


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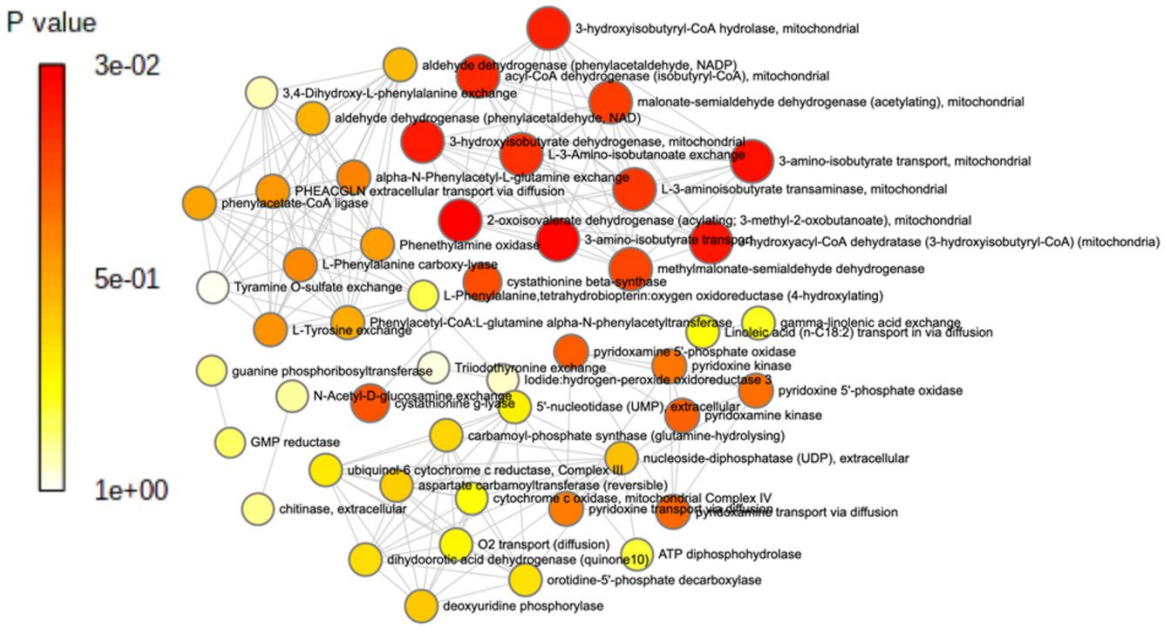


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